

11INVENTOR SEARCH

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FILE 'CASREACT' ENTERED AT 15:29:11 ON 03 APR 2007
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FILE CONTENT:1840 - 1 Apr 2007 VOL 146 ISS 15

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This file contains CAS Registry Numbers for easy and accurate substance identification.

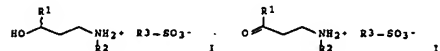
L2 12 SEA FILE=CASREACT ABB=ON MICHEL D7/AU
L3 72 SEA FILE=CASREACT ABB=ON 3-AMINO ALCOHOL#
L4 2 SEA FILE=CASREACT ABB=ON L2 AND L3

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L4 ANSWER 1 OF 2 CASREACT COPYRIGHT 2007 ACS ON STM
ACCESSION NUMBER: 145:271387 CASREACT Full-text
TITLE: Process for the preparation of enantiomerically pure 1-substituted-3-amino alcohols using methyl ketones, primary amines, formaldehydes and sulfonic acids
INVENTOR(S): Brieden, Walter; Clausen, Martin; McGarrity, John; Mettler, Hanspeter; Michel, Dominique
PATENT ASSIGNER(S): Lonza A.-G., Switz.
SOURCE: PCT Int. Appl., 38pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
CLASSIFICATION: 23-15 (Aliphatic Compounds)
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006087166	A1	20060824	WO 2006-EP1334	20060214
M: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,				

GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CP, CG, CI, CH, GA, GN, GO, GM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, WZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KZ, KZ, MD, RU, TJ, TM
EP 1693371 A1 20060823 EP 2005-3657 20050221
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, ES, HU, PL, SK, BA, HR, IS, YU
PRIORITY APPLN. INFO.: MARPAT 145:271387 20050221
OTHER SOURCE(S):
GRAPHIC IMAGE:



ABSTRACT:

Provided is a process for the preparation of N-monosubstituted β -aminoalcs. sulfonates of formula I. Comps. of formula I wherein R1 is (un)substituted C6-20 aryl or (un)substituted C4-12 heteroaryl; R2 is C1-4-alkyl or (un)substituted C6-20 aryl; R3 is selected from the group consisting of C1-18 alkyl, C6-20 cycloalkyl, C6-20 aryl and C7-20 aralkyl residues, and the process for preparing compe. of formula I are claimed. The process comprising the steps of a) reacting a Me ketone, a primary amine, formaldehyde and a sulfonic acid, at a pressure above 1.5 bar, optionally in a organic solvent, said organic solvent optionally containing water, to afford N-monosubstituted β -amino ketone sulfonates of formula II, wherein R1, R2 and R3 are as defined above, and b) asym. hydrogenating said sulfonates in the presence of a base and a catalyst, comprising a transition metal and a diphosphine ligand, in a polar solvent, optionally in the presence of water.

SUPPL. TERM: amino alc sulfonate asym prepn; methyl ketone amine formaldehyde sulfonic acid
INDEX TERM: Ketones, preparation
ROLE: SPN (Synthetic preparation); PREP (Preparation)
(amino; preparation of enantiomerically pure sulfonate salts of substituted amino alcs. and amino ketones by reacting Me ketones, primary amine, formaldehyde and sulfonic acids)
INDEX TERM: Alcohols, preparation
ROLE: SPN (Synthetic preparation); PREP (Preparation)
(chiral, amino; preparation of enantiomerically pure sulfonate salts of substituted amino alcs. and amino ketones by reacting Me ketones, primary amine, formaldehyde and sulfonic acids)
INDEX TERM: Amines, preparation
ROLE: SPN (Synthetic preparation); PREP (Preparation)

10/520362

10/520362

of (keto; preparation of enantiomerically pure sulfonate salts

substituted amino alcs. and amino ketones by reacting Me ketones, primary amine, formaldehyde and sulfonic acids)
INDEX TERM: Asymmetric synthesis and induction

(preparation of enantiomerically pure sulfonate salts of substituted amino alcs. and amino ketones by reacting Me ketones, primary amine, formaldehyde and sulfonic acids)
INDEX TERM: Hydrogenation

Hydrogenation catalysts
(stereoselective; preparation of enantiomerically pure sulfonate salts of substituted amino alcs. and amino ketones by reacting Me ketones, primary amine, formaldehyde and sulfonic acids)
INDEX TERM: 752258-19-8, (R,R,S,S)-TangPhos

ROLE: CAT (Catalyst use); USES (Uses)
(R,R,S,S)-TangPhos, catalyst; preparation of

enantiomerically pure sulfonate salts of substituted amino alcs. and amino ketones by reacting Me ketones, primary amine, formaldehyde and sulfonic acids)
INDEX TERM: 486429-94-1, (S)-C4-TunePhos

ROLE: CAT (Catalyst use); USES (Uses)
(S)-C4-TunePhos, catalyst; preparation of enantiomerically pure sulfonate salts of substituted amino alcs. and amino ketones by reacting Me ketones, primary amine, formaldehyde and sulfonic acids)
INDEX TERM: 136735-95-0, (S,S)-Methyl-DuPHOS

ROLE: CAT (Catalyst use); USES (Uses)
(S,S)-Me-DuPhos, catalyst; preparation of enantiomerically pure sulfonate salts of substituted amino alcs. and amino ketones by reacting Me ketones, primary amine, formaldehyde and sulfonic acids)
INDEX TERM: 7440-16-6, Rhodium, uses 7440-18-8, Ruthenium, uses 133545-16-1 133545-17-2, (S)-MeO-BiPhep 248244-33-9 528814-26-8

ROLE: CAT (Catalyst use); USES (Uses)
(catalyst; preparation of enantiomerically pure sulfonate salts of substituted amino alcs. and amino ketones by reacting Me ketones, primary amine, formaldehyde and sulfonic acids)
INDEX TERM: 863094-23-9P 863094-27-3P 906812-48-4P 906812-49-5P 906812-50-8P 906812-51-9P 906812-52-0P 906812-53-1P 906812-54-2P 906812-55-3P 906812-56-4P 906812-57-5P

ROLE: SPN (Synthetic preparation); PREP (Preparation)
(product; preparation of enantiomerically pure sulfonate salts of substituted amino alcs. and amino ketones by reacting Me ketones, primary amine, formaldehyde and sulfonic acids)
INDEX TERM: 50-00-0, Formaldehyde, reactions 88-15-3, 2-Acetylthiophene 104-15-4, p-Toluenesulfonic acid, reactions 110-88-3, 1,3,5-Trioxane, reactions 3144-16-9, (-)-Camphor-10-sulfonic acid 30525-89-4, Paraformaldehyde 116539-55-0 116539-57-2 206872-28-8, Methylammonium methanesulfonate 645411-16-1, 3-(Methylamino)-1-(2-thienyl)propan-1-one hydrochloride 863094-39-7 863094-46-6

ROLE: RCT (Reactant); RACT (Reactant or reagent)
(starting material; preparation of enantiomerically pure sulfonate salts of substituted amino alcs. and amino ketones by reacting Me ketones, primary amine, formaldehyde and sulfonic acids)
INDEX TERM: 50-00-0, Formaldehyde, reactions 88-15-3, 2-Acetylthiophene 104-15-4, p-Toluenesulfonic acid, reactions 110-88-3, 1,3,5-Trioxane, reactions 3144-16-9, (-)-Camphor-10-sulfonic acid 30525-89-4, Paraformaldehyde 116539-55-0 116539-57-2 206872-28-8, Methylammonium methanesulfonate 645411-16-1, 3-(Methylamino)-1-(2-thienyl)propan-1-one hydrochloride 863094-39-7 863094-46-6

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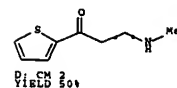
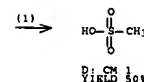
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sulfonate salts of substituted amino alcs. and amino ketones by reacting Me ketones, primary amine, formaldehyde and sulfonic acids)
REFERENCE COUNT: 6
THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD.

REFERENCE(S):
(1) Eli Lilly; EP 0457559 A 1991 CAPLUS
(2) Fujisawa Pharmaceutical; JP 05070412 A 1993 CAPLUS
(3) Lonza; WO 200405239 A 2004 CAPLUS
(4) Mannich, C; BERICHTE DER DEUTSCHEN CHEMISCHEN GESELLSCHAFT 1922, V55, P356
(5) Sakuraba, S; CHEMICAL AND PHARMACEUTICAL BULLETIN 1995, V43(5), P748 CAPLUS
(6) Wilkerson, W; US 4948813 A 1990 CAPLUS

RX(1) OF 6 A + B + C ==> D



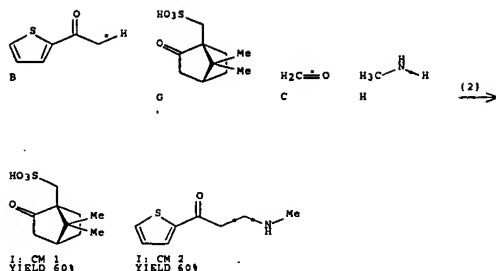
RX(1) RCT A 206872-28-8, B 88-15-3, C 50-00-0

STAGE(1)
SOL 64-17-5 EtOH
CON 3 hours, 120 deg C, 4.5 bar

STAGE(2)
SOL 64-17-5 EtOH, 141-78-6 AcOEt
CON 30 minutes, 25 deg C

PRO D 906812-48-4
NTE paraformaldehyde used, autoclave used, analogs prepd. similarly, thermal

RX(2) OF 6 B + G + C + H ==> I



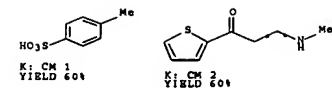
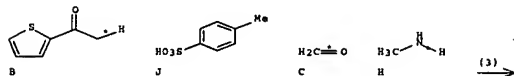
RX(2) RCT B 88-15-3, G 3144-16-9, C 50-00-0, H 74-89-5

STAGE(1)
SOL 64-17-5 EtOH
CON 4 hours, 120 deg C, 4.5 - 4.8 bar

STAGE(2)
SOL 64-17-5 EtOH, 141-78-6 AcOEt
CON 30 minutes, 25 deg C

PRO I 906812-50-8
NTE paraformaldehyde used, autoclave used, thermal

RX(3) OF 6 B + J + C + H ==> K



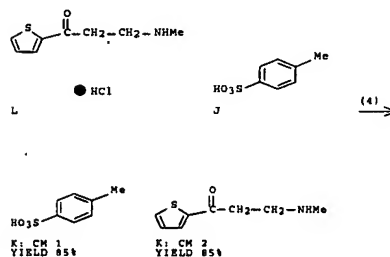
RX(3) RCT B 88-15-3, J 104-15-4, C 50-00-0, H 74-89-5

STAGE(1)
SOL 64-17-5 EtOH
CON 4 hours, 120 deg C

STAGE(2)
SOL 64-17-5 EtOH, 141-78-6 AcOEt
CON 30 minutes, 25 deg C

PRO K 863094-23-9
NTE paraformaldehyde used, autoclave used, thermal

RX(4) OF 6 L + J ==> K



RX(4) RCT L 645411-16-1

STAGE(1)
RGT M 1310-73-2 NaOH
SOL 7732-18-5 Water, 1634-04-4 t-BuOMe
CON SUBSTAGE(1) 15 minutes, 5 deg C
SUBSTAGE(2) 10 minutes, 5 deg C

STAGE(2)
RCT J 104-15-4
SOL 67-56-1 MeOH
CON SUBSTAGE(1) 15 minutes, 5 deg C

5

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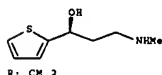
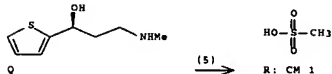
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SUBSTAGE(2) 30 minutes, 25 deg C

PRO K 863094-23-9
NTE analogs prepd. similarly

RX(5) OF 6 Q ==> R

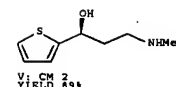


RX(5) RCT Q 116539-55-0

STAGE(1)
RGT S 584-08-7 K2CO3
CAT 528814-26-8 1,1'-Bi-1H-isophosphindole,
2,2'-bis(1,1-dimethylethyl)-2,2',3,3'-tetrahydro-,
(1R,1'R,2S,2'S)-
SOL 7732-18-5 Water, 67-56-1 MeOH
CON room temperature

STAGE(2)
RGT T 1333-74-0 H2
CON 21 hours, 40 deg C, 10 bar

PRO R 906812-56-4
NTE analogs prepd. similarly, autoclave used, high pressure,
stereoselective



RX(6) RCT Q 116539-55-0, G 3144-16-9

STAGE(1)
SOL 64-17-5 EtOH, 141-78-6 AcOEt
CON SUBSTAGE(1) 40 minutes, 30 deg C
SUBSTAGE(2) 15 minutes, 50 deg C

STAGE(2)
SOL 141-78-6 AcOEt
CON SUBSTAGE(1) 15 minutes, reflux
SUBSTAGE(2) 30 minutes, reflux -> 25 deg C

PRO V 906812-57-5

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L4 ANSWER 2 OF 2 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 143:248273 CASREACT Full-text
TITLE: Preparation of enantiomerically pure 1-substituted-
3-amino alcohols
INVENTOR(S): Michel, Dominique
PATENT ASSIGNEE(S): Lonza A.-G., Switz.
SOURCE: Eur. Pat. Appl., 14 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
INT. PATENT CLASSIF.:
MAIN: C07D333-20
SECONDARY: C07D333-22; C07C213-00; C07B053-00
CLASSIFICATION: 27-8 (Heterocyclic Compounds (One Hetero Atom))
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1566383	A1	20050824	EP 2004-3809	20040219
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IS, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, SK, HU, SK				
AU 2005215906	A1	20050901	AU 2005-215906	20050221
CA 2556891	A1	20050901	CA 2005-2556891	20050221
WO 2005080370	A1	20050901	WO 2005-EP1781	20050221
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GR, GU, HD, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LU, LV, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				

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RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GO, GW, ML, MR, NE, SN, TD, TG

EP 1720852 A1 20061115 EP 2005-715425 20050221

R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR

CN 1922168 A 20070228 CN 2005-8005452 20050221

NO 200604017 A 20060915 NO 2006-4017 20060906

PRIORITY APPLN. INFO.: EP 2004-3809 20040219

WO 2004-10043 20040428

WO 2005-EP1781 20050221

OTHER SOURCE(S): MARPAT 143:248273

ABSTRACT:

Provided is a process for the preparation of enantiomerically pure 1-substituted-3-amino alcs. (R)- or (S)-HOCH(R1)CH2CH2NHR2 (R1 = 2-thienyl, 2-furanyl, Ph, substituted 2-thienyl, substituted 2-furanyl, substituted Ph; R2 = Cl-C4-alkyl, Ph, substituted Cl-C4-alkyl, substituted Ph), particularly (S)-(-)- and (R)-(+)-3-N-methylamino-1-(2-thienyl)-1-propanol, by asym. hydrogenating salts of R1COCH2CH2NHR2 using Rh and an asym. ligand.

SUPPL. TERM: alc amino asym prep rhodium chiral ligand hydrogenation; hydrogenation asym amino ketone amino alc prep

INDEX TERM: Alcohols, preparation

ROLE: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)

(amino; asym. synthesis of 1-substituted -3-amino alcs. via hydrogenation of amino ketones)

INDEX TERM: Ketones, reactions

ROLE: RCT (Reactant); RACT (Reactant or reagent)

(amino; asym. synthesis of 1-substituted -3-amino alcs. via hydrogenation of amino ketones)

INDEX TERM: Asymmetric synthesis and induction

(asym. synthesis of 1-substituted -3-amino alcs. via hydrogenation of amino ketones)

INDEX TERM: Amines, reactions

ROLE: RCT (Reactant); RACT (Reactant or reagent)

(keto; asym. synthesis of 1-substituted -3-amino alcs. via hydrogenation of amino ketones)

INDEX TERM: Hydrogenation

(stereoselective; asym. synthesis of 1-substituted -3-amino alcs. via hydrogenation of amino ketones)

INDEX TERM: 116539-55-OP, (S)-(-)-3-(N-Methylamino)-1-(2-thienyl)-1-propanol 116539-57-2P 863094-39-7P 863094-46-6P

ROLE: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)

(asym. synthesis of 1-substituted -3-amino alcs. via hydrogenation of amino ketones)

INDEX TERM: 88-15-3, 2-Acetylthiophene

ROLE: RCT (Reactant); RACT (Reactant or reagent)

(asym. synthesis of 1-substituted -3-amino alcs. via hydrogenation of amino ketones)

INDEX TERM: 569687-76-9P 645411-16-1P, 3-(N-Methylamino)-1-(2-thienyl)-1-propanone hydrochloride 863094-06-8P 863094-15-9P 863094-23-9P 863094-31-9P

ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(asym. synthesis of 1-substituted -3-amino alcs. via hydrogenation of amino ketones)

INDEX TERM: 133545-16-1 133545-17-2 136735-95-0 248244-33-9

486429-94-1 752258-19-8

ROLE: RGT (Reagent); RACT (Reactant or reagent)

(asym. synthesis of 1-substituted -3-amino alcs. via hydrogenation of amino ketones)

INDEX TERM: 116539-56-1P 863094-12-6P 863094-19-3P 863094-27-3P 863094-35-3P

ROLE: SPN (Synthetic preparation); PREP (Preparation)

(asym. synthesis of 1-substituted -3-amino alcs. via hydrogenation of amino ketones)

REFERENCE COUNT: 10

THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD.

REFERENCE(S): (1) Becker, H; WISSENSCHAFTLICHE ZEITSCHRIFT DER TECHNISCHEN HOCHSCHULE FUR CHEMIE 1969, VII(1), P38

(2) Fujisawa Pharm Co Ltd; JP 05070412 A 1993 CAPLUS

(3) Jue, A; WO 03070720 A 2003 CAPLUS

(4) Lilly Co Eli; EP 0457559 A 1991 CAPLUS

(5) Lonza Ag; WO 2004005239 A 2004 CAPLUS

(6) Lonza Ag; WO 2004005307 A 2004 CAPLUS

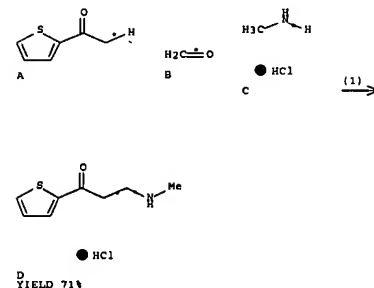
(7) Michael, R; US 6008412 A 1999 CAPLUS

(8) Robertson, D; JOURNAL OF MEDICINAL CHEMISTRY 1988, P1412 CAPLUS

(9) Sakai, K; TETRAHEDRON: ASYMMETRY 2003, VI4(12), P1631 CAPLUS

(10) Sakuraba, S; CHEMICAL AND PHARMACEUTICAL BULLETIN 1995, V43(5), P748 CAPLUS

RX(1) OF 31 A + B + C ==> D...



RX(1) RCT A 88-15-3, B 50-00-0, C 593-51-1

PRO D 645411-16-1

SOL 64-17-5 EtOH

CON SUBSTAGE(1) 9 hours, 120 - 130 deg C

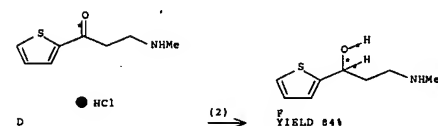
SUBSTAGE(2) 130 deg C -> 20 deg C

NTE paraformaldehyde used, autoclave used

9

10

RX(2) OF 31 ...D ==> F



RX(2) RCT D 645411-16-1

STAGE(1)

RGT G 1310-73-2 NaOH

SOL 7732-18-5 Water, 64-17-5 EtOH

CON 5 minutes, 4 deg C

STAGE(2)

RGT H 16940-66-2 NaBH4

CON SUBSTAGE(1) 30 minutes, 4 deg C

SUBSTAGE(2) 4 hours, 4 deg C

STAGE(3)

RGT I 67-64-1 Me2CO

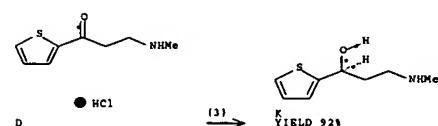
CON SUBSTAGE(1) 5 minutes

SUBSTAGE(2) 10 minutes

PRO F 116539-56-1

NTE incremental addition of sodium borohydride in second stage

RX(3) OF 31 ...D ==> K



RX(3) RCT D 645411-16-1

STAGE(1)

RGT G 1310-73-2 NaOH

SOL 67-56-1 MeOH

CON room temperature

STAGE(2)

SOL 67-56-1 MeOH

CON SUBSTAGE(1) room temperature

SUBSTAGE(2) room temperature -> 50 deg C

STAGE(3)

RGT L 1333-74-0 H2

CON SUBSTAGE(1) 50 deg C, 30 bar

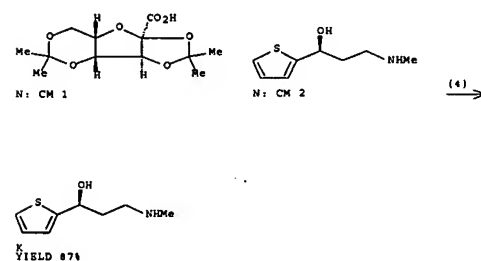
SUBSTAGE(2) 5 hours, 50 deg C

SUBSTAGE(3) 50 deg C -> room temperature

PRO K 116539-55-0

NTE [Rh((S,S)-Me-Duphos)]BF4 used as catalyst stage 2, stereoselective, autoclave used, high pressure in last stage, ee = 97%, optimized on catalyst

RX(4) OF 31 ...N ==> K



RX(4) RCT N 569687-76-9

RGT G 1310-73-2 NaOH

PRO K 116539-55-0

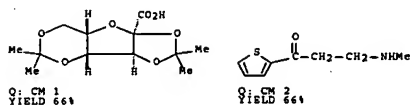
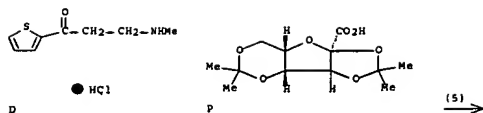
SOL 7732-18-5 Water, 75-09-2 CH2Cl2

CON SUBSTAGE(1) room temperature

SUBSTAGE(2) 15 minutes, room temperature

NTE incremental addition of reactant

RX(5) OF 31 ...D + P ==> Q...



RX(5) RCT D 645411-16-1

STAGE(1)

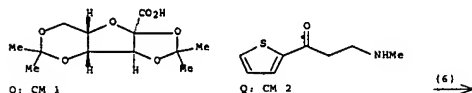
RGT Q 1310-73-2 NaOH
 SOL 7732-18-5 Water, 1634-04-4 t-BuOMe
 CON SUBSTAGE(1) room temperature → 0 deg C
 SUBSTAGE(2) 15 minutes, 0 deg C
 SUBSTAGE(3) 10 minutes, 0 deg C

STAGE(2)

RCT P 18467-77-1
 SOL 1634-04-4 t-BuOMe
 CON room temperature

PRO Q 863094-06-8
 NTE scalable

RX(6) OF 31 ...Q ==> N...



13

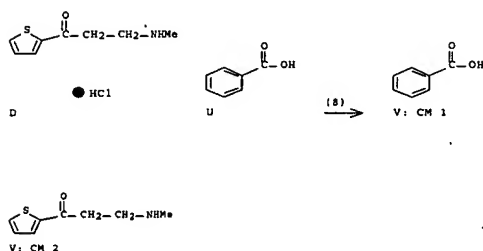
SOL 7732-18-5 Water, 1634-04-4 t-BuOMe
 CON SUBSTAGE(1) room temperature → 10 deg C
 SUBSTAGE(2) 5 - 10 deg C
 SUBSTAGE(3) 15 minutes, 5 - 10 deg C

STAGE(2)

RCT S 526-98-7
 SOL 1634-04-4 t-BuOMe
 CON 15 minutes, <10 deg C

PRO T 863094-12-6

RX(8) OF 31 ...D + U ==> V...



RX(8) RCT D 645411-16-1

STAGE(1)

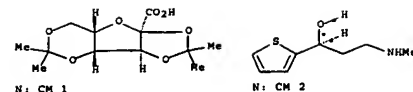
RGT Q 1310-73-2 NaOH
 SOL 7732-18-5 Water, 1634-04-4 t-BuOMe
 CON SUBSTAGE(1) room temperature → 10 deg C
 SUBSTAGE(2) 5 - 10 deg C
 SUBSTAGE(3) 15 minutes, 5 - 10 deg C

STAGE(2)

RCT U 65-85-0
 SOL 1634-04-4 t-BuOMe
 CON 15 minutes, <10 deg C

PRO V 863094-15-9

RX(9) OF 31 ...V ==> W



RX(6) RCT Q 863094-06-8

STAGE(1)

SOL 67-56-1 MeOH
 CON SUBSTAGE(1) room temperature
 SUBSTAGE(2) room temperature
 SUBSTAGE(3) 50 deg C → 50 deg C

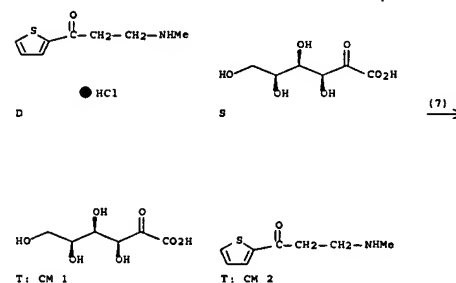
STAGE(2)

RGT L 1333-74-0 H2
 CON SUBSTAGE(1) 50 deg C, 30 bar
 SUBSTAGE(2) 5 hours, 50 deg C
 SUBSTAGE(3) 50 deg C → room temperature

PRO N 569687-76-9

NTE [Rh((R,R,S,S)-tangspos)(norbornadiene)]BF4 used as catalyst
 stage 1, stereoselective, high pressure in last stage, autoclave used, ee = 95%, conversion is 100%

RX(7) OF 31 ...D + S ==> T

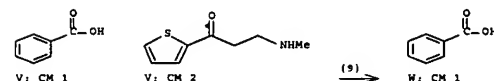


RX(7) RCT D 645411-16-1

STAGE(1)

RGT G 1310-73-2 NaOH

14



RX(9) RCT V 863094-15-9

STAGE(1)

CAT 205064-10-4 Rhodium(1+), [(1,2,5,6-η)-1,5-cyclooctadiene][(2S,2'S,5S,5'S)-1,1'-(1,2-phenylene)bis(2,5-dimethylphospholane-κP)]-, tetrafluoroborate(1-)
 SOL 67-56-1 MeOH
 CON SUBSTAGE(1) room temperature
 SUBSTAGE(2) room temperature → 50 deg C

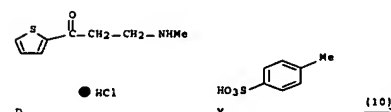
STAGE(2)

RGT L 1333-74-0 H2
 CON SUBSTAGE(1) 50 deg C, 30 bar
 SUBSTAGE(2) 5 hours, 50 deg C
 SUBSTAGE(3) 50 deg C → room temperature

PRO W 863094-19-3

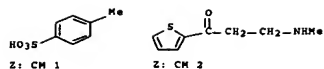
NTE stereoselective, high pressure in last stage, autoclave used, ee = 96.7%, conversion is 99%

RX(10) OF 31 ...D + Y ==> Z...



15

16



RX(10) RCT D 645411-16-1

STAGE(1)

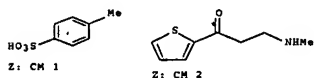
RGT G 1310-73-2 NaOH
 SOL 7732-18-5 Water, 1634-04-4 t-BuOMe
 CON SUBSTAGE(1) room temperature -> 10 deg C
 SUBSTAGE(2) 5 - 10 deg C
 SUBSTAGE(3) 15 minutes, 5 - 10 deg C

STAGE(2)

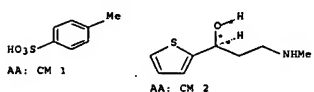
RCT Y 104-15-4
 SOL 1634-04-4 t-BuOMe
 CON 15 minutes, <10 deg C

PRO Z 863094-23-9

RX(11) OF 31 ...Z ==> AA



(11)



RX(11) RCT Z 863094-23-9

STAGE(1)

CAT 205064-10-4 Rhodium(1+), [(1,2,5,6-η)-1,5-cyclooctadiene][(2S,2'S,5S,5'S)-1,1'-(1,2-phenylene)bis[2,5-dimethylphospholane-κP]]-, tetrafluoroborate(1-)
 SOL 67-56-1 MeOH
 CON SUBSTAGE(1) room temperature
 SUBSTAGE(2) room temperature -> 50 deg C

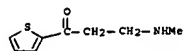
STAGE(2)

RGT L 1333-74-0 H2
 CON SUBSTAGE(1) 50 deg C, 30 bar
 SUBSTAGE(2) 5 hours, 50 deg C
 SUBSTAGE(3) 50 deg C -> room temperature

PRO AA 863094-27-3

NTE stereoselective, high pressure in last stage, autoclave used, ee = 90%, conversion is 5%

RX(12) OF 31 ...D + AB ==> AC...



● HCl

HO2C-(CH2)10-Me

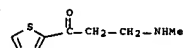
(12)

D

AB

HO2C-(CH2)10-Me

AC: CM 1



RX(12) RCT D 645411-16-1

STAGE(1)

RGT G 1310-73-2 NaOH
 SOL 7732-18-5 Water, 1634-04-4 t-BuOMe
 CON SUBSTAGE(1) room temperature -> 10 deg C
 SUBSTAGE(2) 5 - 10 deg C
 SUBSTAGE(3) 15 minutes, 5 - 10 deg C

STAGE(2)

RCT AB 143-07-7
 SOL 1634-04-4 t-BuOMe
 CON SUBSTAGE(1) 15 minutes, <10 deg C
 SUBSTAGE(2) 1 hour

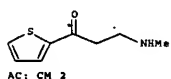
PRO AC 863094-31-9

RX(13) OF 31 ...AC ==> AD

17

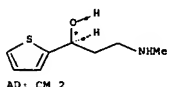
18

HO2C-(CH2)10-Me
 AC: CM 1



(13)

HO2C-(CH2)10-Me
 AD: CM 1



RX(13) RCT AC 863094-31-9

STAGE(1)

SOL 67-56-1 MeOH
 CON SUBSTAGE(1) room temperature
 SUBSTAGE(2) room temperature -> 50 deg C

STAGE(2)

RGT L 1333-74-0 H2
 CON SUBSTAGE(1) 50 deg C, 30 bar
 SUBSTAGE(2) 5 hours, 50 deg C
 SUBSTAGE(3) 50 deg C -> room temperature

PRO AD 863094-35-3

NTE stereoselective, high pressure in last stage, autoclave used, ee = 93.6%, conversion is 100%

10/520362

10/520362

REACTION SEARCH

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FILE CONTENT:1840 - 1 Apr 2007 VOL 146 ISS 15

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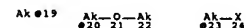
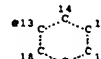
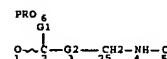
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This file contains CAS Registry Numbers for easy and accurate substance identification.

>> d stat que l27

L15

STR



VAR G1=19/20/23/13

REP G2=(0-2) CH2

NODE ATTRIBUTES:

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NSPEC IS RC AT 11

CONNECT IS E1 RC AT 1

CONNECT IS E1 RC AT 9

CONNECT IS E1 RC AT 19

CONNECT IS E1 RC AT 22

DEFAULT MLEVEL IS ATOM

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DEFAULT ELEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 25

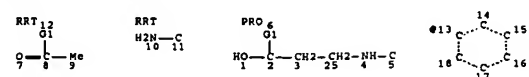
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STEREO ATTRIBUTES: NONE

****MAPPINGS****

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 11 C RRT 5 C PRO
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 L24 STR



AK #19 AK-O-AK #20 21 22 AK-X #23 24

VAR G1-19/20/23/13

NODE ATTRIBUTES:

NSPEC IS RC AT 5
 NSPEC IS RC AT 11
 CONNECT IS E1 RC AT 19
 CONNECT IS E1 RC AT 22
 DEFAULT MLEVEL IS ATOM
 MLEVEL IS CLASS AT 1
 DEFAULT ELEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED
 NUMBER OF NODES IS 25

STEREO ATTRIBUTES: NONE

****MAPPINGS****

NOD SYM ROL NOD SYM ROL
 5 C PRO 11 C RRT
 11 C RRT 5 C PRO
 L27 8 SEA FILE=CASREACT SUB=L19 SSS FUL L24 (26 REACTIONS)

100.0% DONE 219 VERIFIED 26 HIT RXNS 8 DOCS
 SEARCH TIME: 00.00.03

==> d iall 127 1-8; fil hom

L27 ANSWER 1 OF 8 CASREACT COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 146:62451 CASREACT Full-Text
 TITLE: Method for synthesis of 3-methylamino-1-phenylpropanol
 INVENTOR(S): Yang, Guoming; Huang, Shengjian; Chen, Xia
 PATENT ASSIGNEE(S): Shangyu Zhongke Baiyun Fine Chemical Research Center Co., Ltd., Peop. Rep. China
 SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 10 pp.
 DOCUMENT TYPE: Patent
 LANGUAGE: Chinese

21

CLASSIFICATION: 25-7 (Benzene, Its Derivatives, and Condensed

Benzenoid Compounds)

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1865226	A	20061122	CN 2006-10052037	20060619
PRIORITY APPLN. INFO.:			CN 2006-10052037	20060619

ABSTRACT:

The title method comprises the steps: (1) dissolving hypnone, paraformaldehyde and monomethylamine hydrochloride in alc. in an autoclave kettle, heating to 60-100°, concentrating the solution after the reaction, cooling and crystallizing to obtain 3-methylamino-1-phenylpropanone hydrochloride; (2) reducing in the solvent with the catalyst to obtain 3-methylamino-1-phenylpropanol hydrochloride solution; (3) adjusting pH to 9-14 with a base solution, extracting, recycling the solvent and recrystg. with cyclohexane to obtain 3-methylamino-1-phenylpropanol. In step 2, the catalyst is Raney-Ni, the hydrogen pressure is 0.3-1.5 MPa, temperature 25-80°. The method has the advantages of high product yield and quality, low cost and less wastes.

SUPPL. TERM: methylaminophenylpropanol prep hypnone paraformaldehyde

monomethylamine hydrochloride catalytic hydrogenation

INDEX TERM: Hydrogenation

(synthesis of methylaminophenylpropanol from hypnone,

paraformaldehyde and monomethylamine hydrochloride via

catalytic hydrogenation)

INDEX TERM: 7440-02-0, Raney-Nickel, uses

ROLE: CAT (Catalyst use); USES (Uses)

(catalyst; synthesis of methylaminophenylpropanol from

hypnone, paraformaldehyde and monomethylamine

hydrochloride via catalytic hydrogenation)

INDEX TERM: 64-17-5, Ethanol, uses 67-56-1, Methanol, uses 67-63-0,

Isopropanol, uses 110-82-7, Cyclohexane, uses

ROLE: NUU (Other use, unclassified); USES (Uses)

(synthesis of methylaminophenylpropanol from hypnone,

paraformaldehyde and monomethylamine hydrochloride via

catalytic hydrogenation)

INDEX TERM: 98-86-2, Hypnone, reactions 593-51-1, Methylamine

hydrochloride 30525-89-4, Paraformaldehyde

ROLE: RCT (Reactant); RACT (Reactant or reagent)

(synthesis of methylaminophenylpropanol from hypnone,

paraformaldehyde and monomethylamine hydrochloride via

catalytic hydrogenation)

INDEX TERM: 2538-50-3P

ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP

(Preparation); RACT (Reactant or reagent)

(synthesis of methylaminophenylpropanol from hypnone,

paraformaldehyde and monomethylamine hydrochloride via

catalytic hydrogenation)

INDEX TERM: 42142-52-9P, 3-Methylamino-1-phenylpropanol

ROLE: SPN (Synthetic preparation); PREP (Preparation)

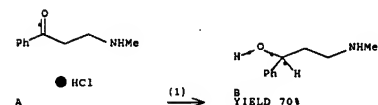
(synthesis of methylaminophenylpropanol from hypnone,

paraformaldehyde and monomethylamine hydrochloride via

catalytic hydrogenation)

RX(1) OF 3 ...A ==> B

22



RX(1) RCT A 2538-50-3

STAGE(1)

RGT C 1333-74-0 H2
 CAT 7440-02-0 Ni
 SOL 7732-18-5 Water
 CON 70 deg C, 1 MPa

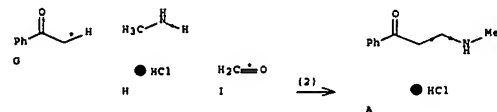
STAGE(2)

RGT D 1310-73-2 NaOH
 SOL 7732-18-5 Water
 CON pH 11

PRO B 42142-52-9

NTS Raney Nickel used, optimization study, optimized on pH,
 stoichiometry, pressure, temperature

RX(2) OF 3 G + H + I ==> A...



RX(2) RCT G 98-86-2, H 593-51-1, I 50-00-0

PRO A 2538-50-3

SOL 64-17-5 EtOH

CON 90 deg C

NTS Mannich reaction, optimization study, optimized on
 stoichiometry, temperature, paraformaldehyde used

L27 ANSWER 2 OF 8 CASREACT COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 142:481782 CASREACT Full-Text

TITLE: Practical synthesis of enantiopure gamma-amino alcohols by rhodium-catalyzed asymmetric hydrogenation of beta-secondary-amino ketones
 AUTHOR(S): Liu, Duan; Gao, Wenzhong; Wang, Chunjiang; Zhang, Xumu
 CORPORATE SOURCE: Department of Chemistry, The Pennsylvania State University, University Park, PA, 16802, USA

23

SOURCE: Angewandte Chemie, International Edition (2005),

44(11), 1687-1689

CODEN: ACIEF5; ISSN: 1433-7851

PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA

DOCUMENT TYPE: Journal

LANGUAGE: English

CLASSIFICATION: 25-7 (Benzene, Its Derivatives, and Condensed

Benzenoid Compounds)

Section cross-reference(s): 27

ABSTRACT:

Several beta-secondary amino ketone hydrochlorides were hydrogenated with remarkably high enantioselectivities by using a rhodium complex containing P-chiral bisphospholane. These results establish a short and practical means for the synthesis of enantiopure N-monosubstituted gamma-amino alcs., which are key intermediates in the synthesis of important antidepressants. For example, the bis[di(methyl)ethyl]tetra(hydro)-1,1'-bi-1H-isophosphindole-rhodium-catalyzed stereoselective hydrogenation of 3-(methylamino)-1-phenyl-1-propanone hydrochloride gave (aS)-u-[2-[(methyl)amino]ethyl]benzenemethanol, which is a synthetic precursor for (yS)-N-methyl-y-[4-(trifluoromethyl)phenoxy]benzenepropanamine [i.e., (S)-fluoxetine]. The synthesis of (aS)-[1-[(methyl)amino]ethyl]thiophenemethanol, a key synthetic intermediate for (S)-duloxetine, was also reported.

SUPPL. TERM: enantiopure aminoalkanol rhodium asym hydrogenation

secondary amino ketone; fluoxetine duloxetine asym synthesis

hydrogenation amino ketone hydrochloride

INDEX TERM: Alcohols, preparation

ROLE: SPN (Synthetic preparation); PREP (Preparation)

(aralkyl, alpha-(aminoalkyl), chiral; preparation of

[(methyl)amino]ethyl]arenemethanol by

tetra(hydro)-1,1'-bi-1H-isophosphindole-rhodium-catalyzed

stereoselective hydrogenation using

(aryl)[(methyl)amino]propanone hydrochloride as synthetic

intermediate)

INDEX TERM: Alcohols, preparation

ROLE: SPN (Synthetic preparation); PREP (Preparation)

(benzyl, alpha-(aminoalkyl), chiral; preparation of

[(methyl)amino]ethyl]arenemethanol deriva. by

1,1'-bi-1H-isophosphindole-rhodium-catalyzed

stereoselective hydrogenation using

(aryl)[(methyl)amino]propanone hydrochloride as synthetic

intermediate)

INDEX TERM: Asymmetric synthesis and induction

(preparation of chiral [(methyl)amino]ethyl]arenemethanol by

bis[di(methyl)ethyl]tetra(hydro)-1,1'-bi-1H-

isophosphindole-rhodium-catalyzed stereoselective

hydrogenation using (aryl)[(methyl)amino]propanone

hydrochloride as synthetic intermediate)

INDEX TERM: Asymmetric synthesis and induction catalysts

(preparation of chiral [(methyl)amino]ethyl]arenemethanol by

tetra(hydro)-1,1'-bi-1H-isophosphindole-rhodium-catalyzed

stereoselective hydrogenation using

(aryl)[(methyl)amino]propanone hydrochloride as synthetic

intermediate)

INDEX TERM: Hydrogenation

Hydrogenation catalysts

(stereoselective; preparation of chiral

[(methyl)amino]ethyl]arenemethanol by

bis[di(methyl)ethyl]tetra(hydro)-1,1'-bi-1H-

24

isophosphindole-rhodium-catalyzed stereoselective hydrogenation using (aryl)((methyl)amino)propanone hydrochloride as synthetic intermediate)

INDEX TERM: Ketones, preparation

ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(α -amino, hydrochlorides; preparation of [(methyl)amino]ethyl]arenemethanols by tetra(hydro)-1,1'-bi-1H-isophosphindole-rhodium-catalyzed stereoselective hydrogenation using α -(alkyl)amino ketone hydrochlorides as synthetic intermediates)

INDEX TERM: 116539-59-4P, (S)-Duloxetine

ROLE: SPN (Synthetic preparation); PREP (Preparation)

(preparation of (S)-duloxetine using (α S)-[(methyl)amino]ethyl]thiophenemethanol as synthetic intermediate)

INDEX TERM: 100568-02-3P, (S)-Fluoxetine

ROLE: SPN (Synthetic preparation); PREP (Preparation)

(preparation of (S)-fluoxetine using (α S)-[(methyl)amino]ethyl]benzenemethanol as synthetic intermediate)

INDEX TERM: 114133-37-8P

ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of (α S)-[(methyl)amino]ethyl]benzenemethanol by bis[di(methyl)ethyl]tetra(hydro)-1,1'-bi-1H-isophosphindole-rhodium-catalyzed stereoselective hydrogenation of [(methyl)amino] (phenyl)-1-propanone hydrochloride)

INDEX TERM: 116539-55-0P

ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of (α S)-[(methyl)amino]ethyl]thiophenemethanol by bis[di(methyl)ethyl]tetra(hydro)-1,1'-bi-1H-isophosphindole-rhodium-catalyzed stereoselective hydrogenation of [(methyl)amino] (thienyl)-1-propanone hydrochloride)

INDEX TERM: 88-15-3, 1-(2-Thienyl)ethanone 93-08-3, 1-(2-Naphthalenyl)ethanone 98-86-2, 1-(Phenyl)ethanone, reactions 99-90-1, 1-(4-Bromophenyl)ethanone 100-06-1, 1-(4-Methoxyphenyl)ethanone 577-16-2, 1-(2-Methylphenyl)ethanone 579-74-8, 1-(2-Methoxyphenyl)ethanone 593-51-1 2142-63-4, 1-(3-Bromophenyl)ethanone 30525-89-4, Paraformaldehyde

ROLE: RCT (Reactant); RACT (Reactant or reagent)

(preparation of [(methyl)amino] (aryl)-1-propanone hydrochloride using paraformaldehyde, (methyl)amine hydrochloride and (aryl)ethanone as starting materials)

INDEX TERM: 3287-99-8

ROLE: RCT (Reactant); RACT (Reactant or reagent)

(preparation of [(phenyl)methyl]amino] (aryl)-1-propanone hydrochloride using paraformaldehyde, (benzyl)amine hydrochloride and (aryl)ethanone as starting materials)

INDEX TERM: 35274-92-1P

ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of chiral [(benzyl)amino]ethyl]arenemethanol by bis[di(methyl)ethyl]tetra(hydro)-1,1'-bi-1H-isophosphindole-rhodium-catalyzed stereoselective

25

hydrogenation using (aryl)((methyl)amino)propanone hydrochloride as synthetic intermediate)

INDEX TERM: 2538-50-3P 24206-62-0P 645411-16-1P 645411-21-8P 851878-34-7P 851878-36-9P 851878-38-1P 851878-40-5P

ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of chiral [(methyl)amino]ethyl]arenemethanol by bis[di(methyl)ethyl]tetra(hydro)-1,1'-bi-1H-isophosphindole-rhodium-catalyzed stereoselective hydrogenation using (aryl)((methyl)amino)propanone hydrochloride as synthetic intermediate)

INDEX TERM: 116539-57-2P 851878-71-2P 851878-74-5P 851878-76-7P 851878-78-9P 851878-80-3P 851878-82-5P 851878-86-9P

ROLE: SPN (Synthetic preparation); PREP (Preparation)

(preparation of chiral [(methyl)amino]ethyl]arenemethanol by bis[di(methyl)ethyl]tetra(hydro)-1,1'-bi-1H-isophosphindole-rhodium-catalyzed stereoselective hydrogenation using (aryl)((methyl)amino)propanone hydrochloride as synthetic intermediate)

INDEX TERM: 850780-91-5 851936-69-1

ROLE: CAT (Catalyst use); USES (Uses)

(preparation of chiral γ -amino alc. derivs. by stereoselective hydrogenation of β -secondary amino ketone derivs. using chiral bis[di(methyl)ethyl]tetra(hydro)-1,1'-bi-1H-isophosphindole-rhodium as catalyst)

INDEX TERM: 34597-73-4P

ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of γ -amino alc. derivative by hydrogenation of [(benzyl)amino] (aryl)-1-propanone hydrochloride derivative)

INDEX TERM: 851878-69-8P

ROLE: SPN (Synthetic preparation); PREP (Preparation)

(preparation of γ -amino alc. derivative by hydrogenation of [(benzyl)amino] (aryl)-1-propanone hydrochloride derivative)

INDEX TERM: 42142-52-9P 69261-99-3P 851878-46-1P 851878-52-9P 851878-56-3P 851878-60-9P

ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

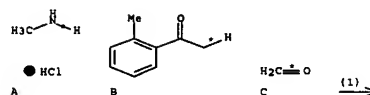
(preparation of γ -amino alc. derivative by hydrogenation of [(methyl)amino] (aryl)-1-propanone hydrochloride derivative)

INDEX TERM: 116539-56-1P 851878-48-3P 851878-50-7P 851878-54-1P 851878-58-5P 851878-62-1P 851878-65-4P 851878-67-6P

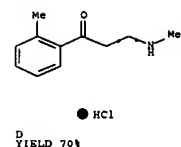
ROLE: SPN (Synthetic preparation); PREP (Preparation)

(preparation of γ -amino alc. derivative by hydrogenation of [(methyl)amino] (aryl)-1-propanone hydrochloride derivative)

RX(1) OF 74 A + B + C ==> D...



26



RX(1) RCT A 593-51-1, B 577-16-2, C 50-00-0

STAGE(1)

RGT E 7647-01-0 HCl
SOL 7732-18-5 Water, 64-17-5 EtOH
CON SUBSTAGE(1) 9 - 20 hours, 110 deg C
SUBSTAGE(2) 110 deg C -> room temperature

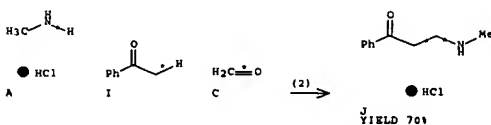
STAGE(2)

SOL 141-78-6 AcOEt
CON 4 hours, room temperature

PRO D 851878-34-7

NTE paraformaldehyde used

RX(2) OF 74 A + I + C ==> J...



RX(2) RCT A 593-51-1, I 98-86-2, C 50-00-0

STAGE(1)

RGT E 7647-01-0 HCl
SOL 7732-18-5 Water, 64-17-5 EtOH
CON SUBSTAGE(1) 9 - 20 hours, 110 deg C
SUBSTAGE(2) 110 deg C -> room temperature

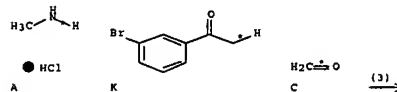
STAGE(2)

SOL 141-78-6 AcOEt
CON 4 hours, room temperature

PRO J 2538-50-3

NTE paraformaldehyde used

RX(3) OF 74 A + K + C ==> L...



L
YIELD 70%

RX(3) RCT A 593-51-1, K 2142-63-4, C 50-00-0

STAGE(1)

RGT E 7647-01-0 HCl
SOL 7732-18-5 Water, 64-17-5 EtOH
CON SUBSTAGE(1) 9 - 20 hours, 110 deg C
SUBSTAGE(2) 110 deg C -> room temperature

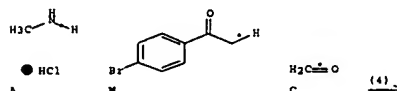
STAGE(2)

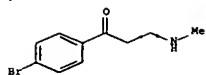
SOL 141-78-6 AcOEt
CON 4 hours, room temperature

PRO L 851878-36-9

NTE paraformaldehyde used

RX(4) OF 74 A + M + C ==> N...





● HCl

N
YIELD 70%

RX(4) RCT A 593-51-1, M 99-90-1, C 50-00-0

STAGE(1)

RGT E 7647-01-0 HCl

SOL 7732-18-5 Water, 64-17-5 EtOH

CON SUBSTAGE(1) 9 - 20 hours, 110 deg C

SUBSTAGE(2) 110 deg C -> room temperature

STAGE(2)

SOL 141-78-6 AcOEt

CON 4 hours, room temperature

PRO N 851878-38-1

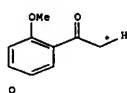
NTE paraformaldehyde used

RX(5) OF 74 A + O + C ==> P...



● HCl

A

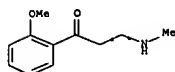


O



C

(5) →



● HCl

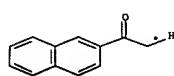
P
YIELD 70%

RX(7) OF 74 A + S + C ==> T...



● HCl

A

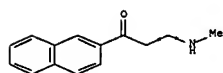


S



C

(7) →



● HCl

T
YIELD 70%

RX(7) RCT A 593-51-1, S 93-08-3, C 50-00-0

STAGE(1)

RGT E 7647-01-0 HCl

SOL 7732-18-5 Water, 64-17-5 EtOH

CON SUBSTAGE(1) 9 - 20 hours, 110 deg C

SUBSTAGE(2) 110 deg C -> room temperature

STAGE(2)

SOL 141-78-6 AcOEt

CON 4 hours, room temperature

PRO T 645411-21-8

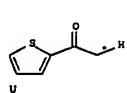
NTE paraformaldehyde used

RX(8) OF 74 A + U + C ==> V...



● HCl

A



U



C

(8) →

RX(5) RCT A 593-51-1, O 579-74-8, C 50-00-0

STAGE(1)

RGT E 7647-01-0 HCl

SOL 7732-18-5 Water, 64-17-5 EtOH

CON SUBSTAGE(1) 9 - 20 hours, 110 deg C

SUBSTAGE(2) 110 deg C -> room temperature

STAGE(2)

SOL 141-78-6 AcOEt

CON 4 hours, room temperature

PRO P 851878-40-5

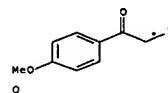
NTE paraformaldehyde used

RX(6) OF 74 A + Q + C ==> R...



● HCl

A

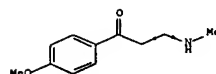


Q



C

(6) →



● HCl

R
YIELD 70%

RX(6) RCT A 593-51-1, Q 100-06-1, C 50-00-0

STAGE(1)

RGT E 7647-01-0 HCl

SOL 7732-18-5 Water, 64-17-5 EtOH

CON SUBSTAGE(1) 9 - 20 hours, 110 deg C

SUBSTAGE(2) 110 deg C -> room temperature

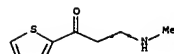
STAGE(2)

SOL 141-78-6 AcOEt

CON 4 hours, room temperature

PRO R 24206-62-0

NTE paraformaldehyde used



● HCl

V
YIELD 70%

RX(8) RCT A 593-51-1, U 88-15-3, C 50-00-0

STAGE(1)

RGT E 7647-01-0 HCl

SOL 7732-18-5 Water, 64-17-5 EtOH

CON SUBSTAGE(1) 9 - 20 hours, 110 deg C

SUBSTAGE(2) 110 deg C -> room temperature

STAGE(2)

SOL 141-78-6 AcOEt

CON 4 hours, room temperature

PRO V 645411-16-1

NTE paraformaldehyde used

RX(9) OF 74 I + W + C ==> X...



I



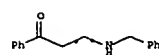
W

● HCl



C

(9) →



● HCl

X
YIELD 70%

RX(9) RCT I 98-86-2, W 3287-99-8, C 50-00-0

STAGE(1)

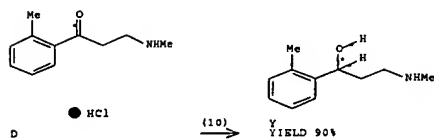
RGT E 7647-01-0 HCl

SOL 7732-18-5 Water, 64-17-5 EtOH
CON SUBSTAGE(1) 9 - 20 hours, 110 deg C
SUBSTAGE(2) 110 deg C -> room temperature

STAGE(2)
SOL 141-78-6 AcOEt
CON 4 hours, room temperature

PRO X 35274-92-1
NTE paraformaldehyde used

RX(10) OF 74 ...D ==> Y...



RX(10) RCT D 851878-34-7

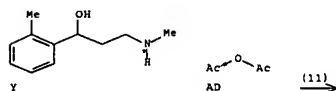
STAGE(1)
RGT Z 16940-66-2 NaBH4
SOL 67-56-1 MeOH
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) 1 hour, room temperature

STAGE(2)
RGT AA 12125-02-9 NH4Cl
SOL 7732-18-5 Water
CON room temperature

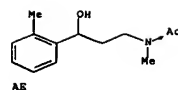
STAGE(3)
RGT AB 1310-73-2 NaOH
SOL 7732-18-5 Water
CON room temperature, basify

PRO Y 851878-46-1

RX(11) OF 74 ...Y + AD ==> AE

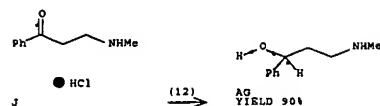


33



RX(11) RCT Y 851878-46-1, AD 108-24-7
PRO AE 851878-48-3
SOL 75-09-2 CH2Cl2
CON 10 minutes, 0 deg C

RX(12) OF 74 ...J ==> AG...



RX(12) RCT J 2538-50-3

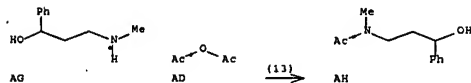
STAGE(1)
RGT Z 16940-66-2 NaBH4
SOL 67-56-1 MeOH
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) 1 hour, room temperature

STAGE(2)
RGT AA 12125-02-9 NH4Cl
SOL 7732-18-5 Water
CON room temperature

STAGE(3)
RGT AB 1310-73-2 NaOH
SOL 7732-18-5 Water
CON room temperature, basify

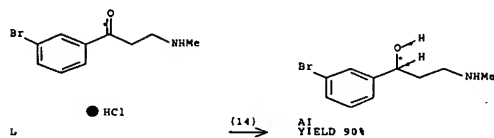
PRO AG 42142-52-9

RX(13) OF 74 ...AG + AD ==> AH



RX(13) RCT AG 42142-52-9, AD 108-24-7
PRO AH 851878-50-7
SOL 75-09-2 CH2Cl2
CON 10 minutes, 0 deg C

RX(14) OF 74 ...L ==> AI...



RX(14) RCT L 851878-36-9

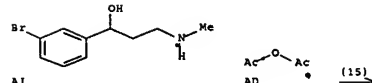
STAGE(1)
RGT Z 16940-66-2 NaBH4
SOL 67-56-1 MeOH
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) 1 hour, room temperature

STAGE(2)
RGT AA 12125-02-9 NH4Cl
SOL 7732-18-5 Water
CON room temperature

STAGE(3)
RGT AB 1310-73-2 NaOH
SOL 7732-18-5 Water
CON room temperature, basify

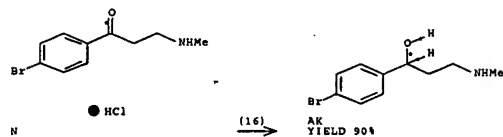
PRO AI 851878-52-9

RX(15) OF 74 ...AI + AD ==> AJ



RX(15) RCT AI 851878-52-9, AD 108-24-7
PRO AJ 851878-54-1
SOL 75-09-2 CH2Cl2
CON 10 minutes, 0 deg C

RX(16) OF 74 ...N ==> AK...



RX(16) RCT N 851878-38-1

STAGE(1)
RGT Z 16940-66-2 NaBH4
SOL 67-56-1 MeOH
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) 1 hour, room temperature

STAGE(2)
RGT AA 12125-02-9 NH4Cl
SOL 7732-18-5 Water
CON room temperature

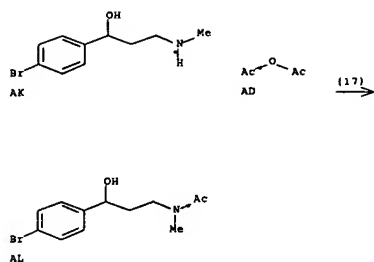
STAGE(3)
RGT AB 1310-73-2 NaOH

35

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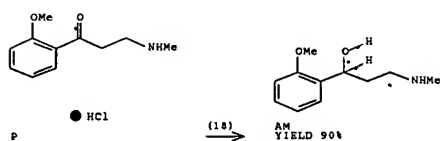
SOL 7732-18-5 Water
CON room temperature, basify
PRO AK 851878-56-3

RX(17) OF 74 ...AK + AD ==> AL



RX(17) RCT AK 851878-56-3, AD 108-24-7
PRO AL 851878-58-5
SOL 75-09-2 CH₂Cl₂
CON 10 minutes, 0 deg C

RX(18) OF 74 ...P ==> AM...



RX(18) RCT P 851878-40-5

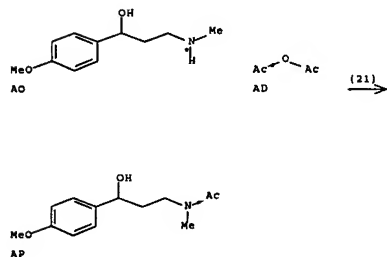
STAGE(1)
RGT Z 16940-66-2 NaBH₄
SOL 67-56-1 MeOH
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) 1 hour, room temperature

STAGE(2)
RGT AA 12125-02-9 NH₄Cl
SOL 7732-18-5 Water
CON room temperature

STAGE(3)
RGT AB 1310-73-2 NaOH
SOL 7732-18-5 Water
CON room temperature, basify

PRO AO 693261-99-3

RX(21) OF 74 ...AO + AD ==> AP



RX(21) RCT AO 693261-99-3, AD 108-24-7
PRO AP 851878-65-4
SOL 75-09-2 CH₂Cl₂
CON 10 minutes, 0 deg C

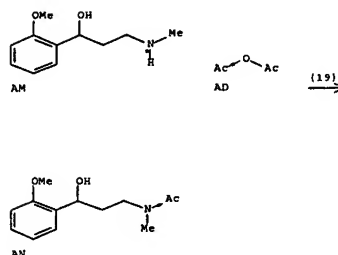
RX(22) OF 74 ...T ==> AO

STAGE(2)
RGT AA 12125-02-9 NH₄Cl
SOL 7732-18-5 Water
CON room temperature

STAGE(3)
RGT AB 1310-73-2 NaOH
SOL 7732-18-5 Water
CON room temperature, basify

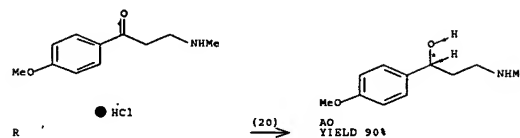
PRO AM 851878-60-9

RX(19) OF 74 ...AM + AD ==> AN



RX(19) RCT AM 851878-60-9, AD 108-24-7
PRO AN 851878-62-1
SOL 75-09-2 CH₂Cl₂
CON 10 minutes, 0 deg C

RX(20) OF 74 ...R ==> AO...



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RX(20) RCT R 24206-62-0

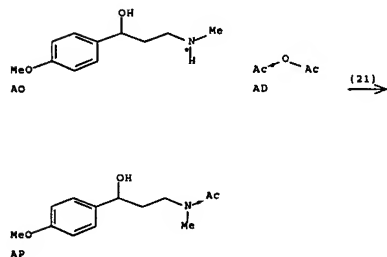
STAGE(1)
RGT Z 16940-66-2 NaBH₄
SOL 67-56-1 MeOH
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) 1 hour, room temperature

STAGE(2)
RGT AA 12125-02-9 NH₄Cl
SOL 7732-18-5 Water
CON room temperature

STAGE(3)
RGT AB 1310-73-2 NaOH
SOL 7732-18-5 Water
CON room temperature, basify

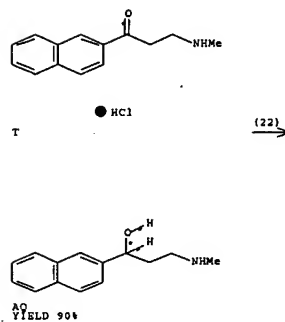
PRO AO 693261-99-3

RX(21) OF 74 ...AO + AD ==> AP



RX(21) RCT AO 693261-99-3, AD 108-24-7
PRO AP 851878-65-4
SOL 75-09-2 CH₂Cl₂
CON 10 minutes, 0 deg C

RX(22) OF 74 ...T ==> AO



RX(22) RCT T 645411-21-8

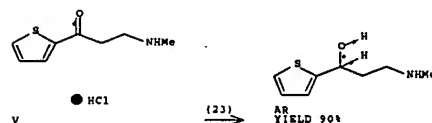
STAGE(1)
RGT Z 16940-66-2 NaBH₄
SOL 67-56-1 MeOH
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) 1 hour, room temperature

STAGE(2)
RGT AA 12125-02-9 NH₄Cl
SOL 7732-18-5 Water
CON room temperature

STAGE(3)
RGT AB 1310-73-2 NaOH
SOL 7732-18-5 Water
CON room temperature, basify

PRO AQ 851878-67-6

RX(23) OF 74 ...V ==> AR



39

40

RX(23) RCT V 645411-16-1

STAGE(1)

RGT Z 16940-66-2 NaBH4
SOL 67-56-1 MeOH
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) 1 hour, room temperature

STAGE(2)

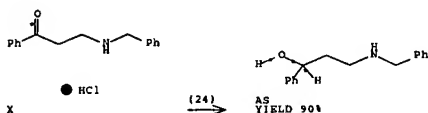
RGT AA 12125-02-9 NH4Cl
SOL 7732-18-5 Water
CON room temperature

STAGE(3)

RGT AB 1310-73-2 NaOH
SOL 7732-18-5 Water
CON room temperature, basify

PRO AR 116539-56-1

RX(24) OF 74 ...X ==> AS...



RX(24) RCT X 35274-92-1

STAGE(1)

RGT Z 16940-66-2 NaBH4
SOL 67-56-1 MeOH
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) 1 hour, room temperature

STAGE(2)

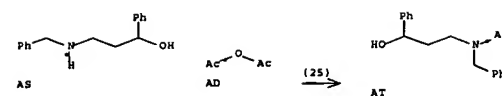
RGT AA 12125-02-9 NH4Cl
SOL 7732-18-5 Water
CON room temperature

STAGE(3)

RGT AB 1310-73-2 NaOH
SOL 7732-18-5 Water
CON room temperature, basify

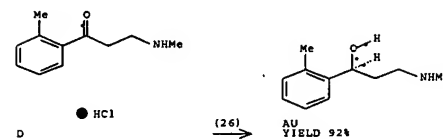
PRO AS 34597-73-4

RX(25) OF 74 ...AS + AD ==> AT



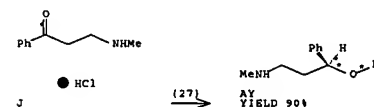
RX(25) RCT AS 34597-73-4, AD 108-24-7
PRO AT 851878-69-8
SOL 75-09-2 CH2Cl2
CON 10 minutes, 0 deg C

RX(26) OF 74 ...D ==> AU



RX(26) RCT D 851878-34-7
RGT AV 584-08-7 K2CO3, AW 1333-74-0 H2
PRO AU 851878-71-2
CAT 851936-69-1 Rhodium(1+), [(2,3,5,6-η)-bicyclo[2.2.1]hepta-2,5-diene][(1S,1'S,2S,2'S)-2,2'-bis(1,1-dimethylethyl)-2,2',3,3'-tetrahydro-1,1'-bi-1H-isophosphindole-κP2,κP2']-, (OC-6-11)-hexafluoroantimonate(1-)
SOL 67-56-1 MeOH
CON 12 hours, 50 deg C, 10 bar
NTE stereoselective, optimization study(optimized on reagent, solvent, pressure)

RX(27) OF 74 ...J ==> AY...



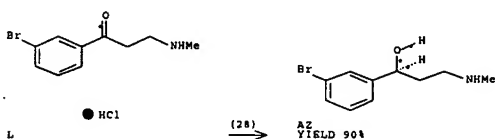
41

42

RX(27) RCT J 2538-50-3

RGT AV 584-08-7 K2CO3, AW 1333-74-0 H2
PRO AY 114133-37-8
CAT 851936-69-1 Rhodium(1+), [(2,3,5,6-η)-bicyclo[2.2.1]hepta-2,5-diene][(1S,1'S,2S,2'S)-2,2'-bis(1,1-dimethylethyl)-2,2',3,3'-tetrahydro-1,1'-bi-1H-isophosphindole-κP2,κP2']-, (OC-6-11)-hexafluoroantimonate(1-)
SOL 67-56-1 MeOH
CON 12 hours, 50 deg C, 10 bar
NTE stereoselective

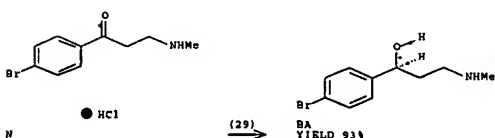
RX(28) OF 74 ...L ==> AZ



RX(28) RCT L 851878-36-9

RGT AV 584-08-7 K2CO3, AW 1333-74-0 H2
PRO AZ 851878-74-5
CAT 851936-69-1 Rhodium(1+), [(2,3,5,6-η)-bicyclo[2.2.1]hepta-2,5-diene][(1S,1'S,2S,2'S)-2,2'-bis(1,1-dimethylethyl)-2,2',3,3'-tetrahydro-1,1'-bi-1H-isophosphindole-κP2,κP2']-, (OC-6-11)-hexafluoroantimonate(1-)
SOL 67-56-1 MeOH
CON 12 hours, 50 deg C, 10 bar
NTE stereoselective

RX(29) OF 74 ...N ==> BA

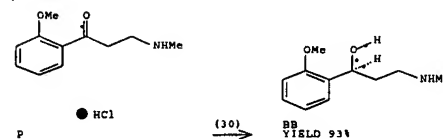


RX(29) RCT N 851878-38-1
RGT AV 584-08-7 K2CO3, AW 1333-74-0 H2

PRO BA 851878-76-7

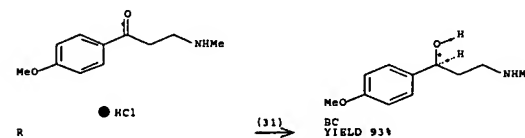
CAT 851936-69-1 Rhodium(1+), [(2,3,5,6-η)-bicyclo[2.2.1]hepta-2,5-diene][(1S,1'S,2S,2'S)-2,2'-bis(1,1-dimethylethyl)-2,2',3,3'-tetrahydro-1,1'-bi-1H-isophosphindole-κP2,κP2']-, (OC-6-11)-hexafluoroantimonate(1-)
SOL 67-56-1 MeOH
CON 12 hours, 50 deg C, 10 bar
NTE stereoselective

RX(30) OF 74 ...P ==> BB



RX(30) RCT P 851878-40-5
RGT AV 584-08-7 K2CO3, AW 1333-74-0 H2
PRO BB 851878-78-9
CAT 851936-69-1 Rhodium(1+), [(2,3,5,6-η)-bicyclo[2.2.1]hepta-2,5-diene][(1S,1'S,2S,2'S)-2,2'-bis(1,1-dimethylethyl)-2,2',3,3'-tetrahydro-1,1'-bi-1H-isophosphindole-κP2,κP2']-, (OC-6-11)-hexafluoroantimonate(1-)
SOL 67-56-1 MeOH
CON 12 hours, 50 deg C, 10 bar
NTE stereoselective

RX(31) OF 74 ...R ==> BC



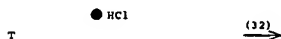
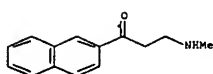
RX(31) RCT R 24206-62-0
RGT AV 584-08-7 K2CO3, AW 1333-74-0 H2
PRO BC 851878-80-3
CAT 851936-69-1 Rhodium(1+), [(2,3,5,6-η)-bicyclo[2.2.1]hepta-2,5-diene][(1S,1'S,2S,2'S)-2,2'-bis(1,1-dimethylethyl)-2,2',3,3'-tetrahydro-1,1'-bi-1H-isophosphindole-κP2,κP2']-,

43

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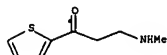
(OC-6-11)-hexafluoroantimonate(1-)
 SOL 67-56-1 MeOH
 CON 12 hours, 50 deg C, 10 bar
 NTE stereoselective

RX(32) OF 74 ...T ==> BD

BD
YIELD 92%

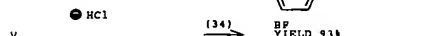
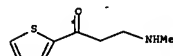
RX(32) RCT T 645411-21-8
 RGT AV 584-08-7 K2CO3, AW 1333-74-0 H2
 PRO BD 851878-82-5
 CAT 851936-69-1 Rhodium(1+), [(2,3,5,6-η)-bicyclo[2.2.1]hepta-2,5-diene] [(1S,1'S,2S,2'S)-2,2'-bis(1,1-dimethylethyl)-2,2',3,3'-tetrahydro-1,1'-bi-1H-isophosphindole-κP2,κP2']-, (OC-6-11)-hexafluoroantimonate(1-)
 SOL 67-56-1 MeOH
 CON 12 hours, 50 deg C, 10 bar
 NTE stereoselective

RX(33) OF 74 ...V ==> BE...

BE
YIELD 93%

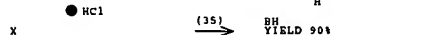
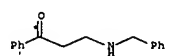
RX(33) RCT V 645411-16-1
 RGT AV 584-08-7 K2CO3, AW 1333-74-0 H2
 PRO BE 116539-55-0
 CAT 851936-69-1 Rhodium(1+), [(2,3,5,6-η)-bicyclo[2.2.1]hepta-2,5-diene] [(1S,1'S,2S,2'S)-2,2'-bis(1,1-dimethylethyl)-2,2',3,3'-tetrahydro-1,1'-bi-1H-isophosphindole-κP2,κP2']-, (OC-6-11)-hexafluoroantimonate(1-)
 SOL 67-56-1 MeOH
 CON 12 hours, 50 deg C, 10 bar
 NTE stereoselective

RX(34) OF 74 ...V ==> BF

BF
YIELD 93%

RX(34) RCT V 645411-16-1
 RGT AV 584-08-7 K2CO3, AW 1333-74-0 H2
 PRO BF 116539-57-2
 CAT 850780-91-5 Rhodium(1+), [(2,3,5,6-η)-bicyclo[2.2.1]hepta-2,5-diene] [(1R,1'R,2R,2'R)-2,2'-bis(1,1-dimethylethyl)-2,2',3,3'-tetrahydro-1,1'-bi-1H-isophosphindole-κP2,κP2']-, (OC-6-11)-hexafluoroantimonate(1-)
 SOL 67-56-1 MeOH
 CON 12 hours, 50 deg C, 10 bar
 NTE stereoselective

RX(35) OF 74 ...X ==> BH

BH
YIELD 90%

RX(35) RCT X 35274-92-1
 RGT AV 584-08-7 K2CO3, AW 1333-74-0 H2
 PRO BH 851878-86-9
 CAT 851936-69-1 Rhodium(1+), [(2,3,5,6-η)-bicyclo[2.2.1]hepta-

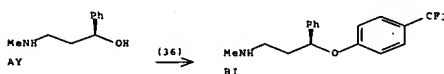
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10/520362

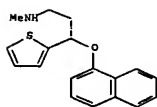
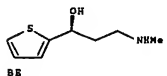
2,5-diene) [(1S,1'S,2S,2'S)-2,2'-bis(1,1-dimethylethyl)-2,2',3,3'-tetrahydro-1,1'-bi-1H-isophosphindole-κP2,κP2']-, (OC-6-11)-hexafluoroantimonate(1-)
 SOL 67-56-1 MeOH
 CON 12 hours, 50 deg C, 10 bar
 NTE stereoselective

RX(36) OF 74 ...AY ==> BI



RX(36) RCT AY 114133-37-8
 PRO BI 100568-02-3
 NTE literature preparation

RX(37) OF 74 ...BE ==> BJ



BJ

RX(37) RCT BE 116539-55-0
 PRO BJ 116539-59-4
 NTE literature preparation

L27 ANSWER 3 OF 8 CASREACT COPYRIGHT 2007 ACS ON STN
 ACCESSION NUMBER: 140:423470 CASREACT Full-text
 TITLE: Synthesis of 3-aminomethyl-1-propanol, a fluoxetine precursor
 INVENTOR(S): Zelenin, Alexander

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10/520362

PATENT ASSIGNER(S): Board of Regents, the University of Texas System, USA
 SOURCE: U.S. Pat. Appl. Publ., 7 pp.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 INT. PATENT CLASSIF.:
 MAIN: C07C225-10
 US PATENT CLASSIF.: 564343000
 CLASSIFICATION: 25-9 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
 Section cross-reference(s): 45, 63

FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004102651	A1	20040527	US 2002-302806	20021122
US 6846957	B2	20050125	US 2002-302806	20021122

PRIORITY APPLN. INFO.:

ABSTRACT:

Fluoxetine hydrochloride is prepared by: (a) synthesizing 1-phenyl-3-methylamino-1-propen-1-one by (i) the claisen condensation of acetophenone with Et formate leading to benzoylacetalddehyde sodium salt, and (ii) the condensation of the benzoylacetalddehyde sodium salt with methylamine hydrochloride; (b) converting 1-phenyl-3-methylamino-2-propen-1-one into 3-methylamino-1-phenyl-1-propanol using sodium borohydride and acetic acid; and (c) converting 3-methylamino-1-phenyl-1-propanol into fluoxetine hydrochloride by treatment with hydrochloric acid.

SUPPL. TERM: fluoxetine hydrochloride prepn; aminomethylpropanol prepn
 INDEX TERM: Condensation reaction

(Claisen; of acetophenone with Et formate to give benzoylacetalddehyde sodium salt)

INDEX TERM: Reduction
 (of 1-phenyl-3-methylamino-1-propen-1-one into 3-methylamino-1-phenyl-1-propanol with NaBH4 in AcOH)

INDEX TERM: Condensation reaction
 (of benzoylacetalddehyde sodium salt with methylamine hydrochloride to give 1-phenyl-3-methylamino-1-propen-1-one)

INDEX TERM: Neutralization
 (of fluoxetine with HCl in ether in the preparation of fluoxetine hydrochloride)

INDEX TERM: Ethers, uses
 ROLE: NUU (Other use, unclassified); USES (Uses)

INDEX TERM: (solvents; for the salification of fluoxetine with HCl)
 64-19-7, Acetic acid, uses

INDEX TERM: ROLE: NUU (Other use, unclassified); USES (Uses)
 (in the preparation of fluoxetine hydrochloride)

INDEX TERM: 98-56-6, 4-Chlorobenzotrifluoride 98-86-2, Acetophenone, reactions 109-94-4, Ethyl formate 593-51-1, Methylamine hydrochloride 1310-71-2, Sodium hydroxide, reactions 7647-01-0, Hydrogen chloride, reactions 16940-66-2, Sodium borohydride

ROLE: RCT (Reactant); RACT (Reactant or reagent)
 (in the preparation of fluoxetine hydrochloride)

INDEX TERM: 877-50-9P 20717-88-8P, Benzoylacetalddehyde sodium salt 42142-52-9P, 3-Methylamino-1-phenyl-1-propanol

ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

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INDEX TERM: (in the preparation of fluoxetine hydrochloride)
54910-89-3P
ROLE: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

INDEX TERM: 56296-78-7P, Fluoxetine hydrochloride
ROLE: SPN (Synthetic preparation); THU (Therapeutic use);
BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of)

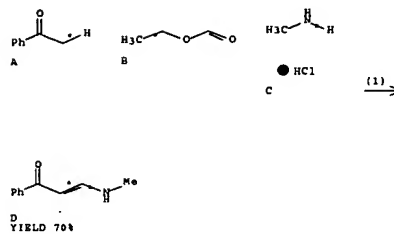
INDEX TERM: 67-68-5, DMSO, uses
ROLE: MUU (Other use, unclassified); USES (Uses)
(solvent; in the preparation of fluoxetine hydrochloride)

REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD.

REFERENCE(S): (1) Ager; Tet. Asymmetry 1997, V8(20), P3327 CAPLUS
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(6) Anon; EP 0529842 1993 CAPLUS
(7) Anon; HU 207035 1993
(8) Anon; WO 9309769 1993 CAPLUS
(9) Anon; WO 9400416 1994 CAPLUS
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(11) Anon; ES 2103681 1997 CAPLUS
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(13) Anon; WO 9905129 1999 CAPLUS
(14) Anon; WO 9906362 1999 CAPLUS
(15) Anon; WO 9967196 1999 CAPLUS
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(55) Young; 1993
(56) Young; US 5708035 A 1998 CAPLUS

RX(1) OF 9 A + B + C ==> D...



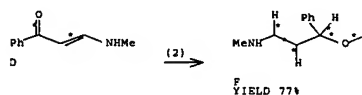
RX(1) RCT A 98-86-2, B 109-94-4

STAGE(1)
CON room temperature

STAGE(2)
RCT C 593-51-1
SOL 7732-18-5 Water
CON room temperature

PRO D 877-50-9
NTE limited exptl. details, Claisen condensation

RX(2) OF 9 ...D ==> F...

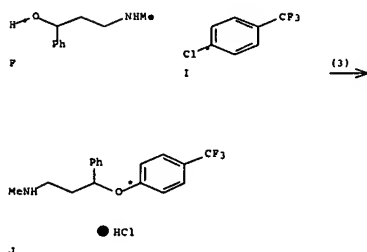


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RX(2) RCT D 877-50-9
RGT G 16940-66-2 NaBH4
PRO F 42142-52-9
SOL 64-19-7 AcOH
CON SUBSTAGE(1) 30 minutes, 5 - 10 deg C
SUBSTAGE(2) 30 minutes, 5 - 10 deg C
SUBSTAGE(3) 3 hours, room temperature

RX(3) OF 9 ...F + I ==> J



RX(3) RCT F 42142-52-9

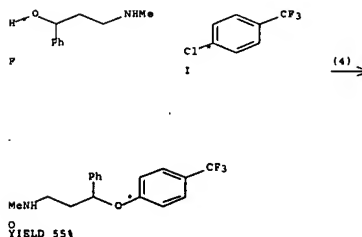
STAGE(1)
RGT K 7646-69-7 NaH
SOL 67-68-5 DMSO
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) 1 hour, room temperature -> 60 deg C

STAGE(2)
RCT I 98-56-6
CON SUBSTAGE(2) 6 hours, 115 deg C
SUBSTAGE(3) 115 deg C -> room temperature

STAGE(3)
RGT E 7732-18-5 Water

STAGE(4)
RGT L 7647-01-0 HCl
SOL 60-29-7 Et2O
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) 30 minutes, room temperature

PRO J 56296-78-7



RX(4) RCT F 42142-52-9

STAGE(1)
RGT K 7646-69-7 NaH
SOL 67-68-5 DMSO
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) 1 hour, room temperature -> 60 deg C

STAGE(2)
RCT I 98-56-6
CON SUBSTAGE(2) 6 hours, 115 deg C
SUBSTAGE(3) 115 deg C -> room temperature

STAGE(3)
RGT E 7732-18-5 Water

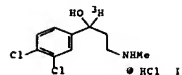
PRO O 54910-89-3

L27 ANSWER 4 OF 8 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 114:5913 CASREACT Full-text
TITLE: Synthesis of tritium labeled 1-(3,4-dichlorophenyl)-3-(methylamino)propanol hydrochloride
AUTHOR(S): Hill, John A.; Wisowaty, James C.
CORPORATE SOURCE: Chem. Dev. Lab., Burroughs Wellcome Co., Research Triangle Park, NC, 27709, USA
SOURCE: Journal of Labelled Compounds and Radiopharmaceuticals (1990), 28(7), 811-18
CODEN: JLCRD4; ISSN: 0362-4803
DOCUMENT TYPE: Journal
LANGUAGE: English
CLASSIFICATION: 25-7 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
GRAPHIC IMAGE:

RX(4) OF 9 ...F + I ==> O

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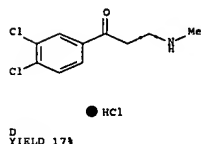
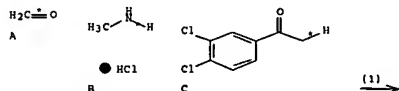
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ABSTRACT:
1-(3,4-Dichlorophenyl)-3-(methylamino)-1-propanol hydrochloride, a potential antidepressant, was synthesized by a two-step method in the [3H]-labeled form I with specific activity 12.5 mCi/mmol suitable for drug metabolism and disposition studies.

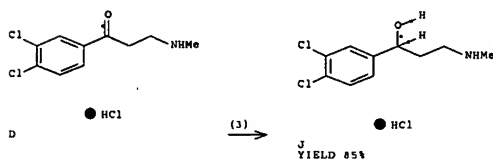
SUPPL. TERM: chlorophenylmethylaminopropanol tritium labeled; propanol chlorophenylmethylamino tritium labeled
INDEX TERM: 2642-63-9
ROLE: RCT (Reactant); RACT (Reactant or reagent) (aminomethylation of)
INDEX TERM: 130826-97-0P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (preparation and reduction of)
INDEX TERM: 2538-50-3P 130826-98-1P 130826-99-2P 130827-00-8P
ROLE: SPN (Synthetic preparation); PREP (Preparation) (preparation of)

RX(1) OF 7 A + B + C ==> D...



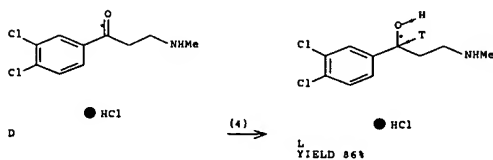
RX(1) RCT A 50-00-0, B 593-51-1, C 2642-63-9
PRO D 130826-97-0

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RX(3) RCT D 130826-97-0
RGT G 16940-66-2 NaBH4
PRO J 130826-99-2
SOL 7732-18-5 Water, 67-63-0 Me2CHOH

RX(4) OF 7 ...D ==> L

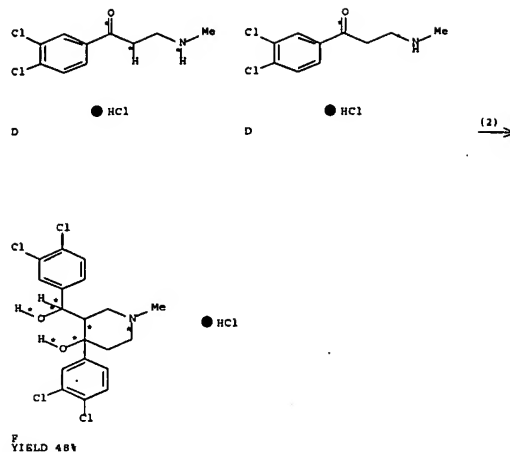


RX(4) RCT D 130826-97-0
RGT G 16940-66-2 NaBH4, M 61113-34-6 NaBH3T
PRO L 130827-00-8
SOL 7732-18-5 Water, 67-63-0 Me2CHOH

L27 ANSWER 5 OF 8 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 108:6119 CASREACT Full-text
TITLE: Carbanion-accelerated Claisen rearrangements. 4. Asymmetric induction via 1,3,2-oxazaphosphorinanes
AUTHOR(S): Denmark, Scott E.; Marlin, John E.
CORPORATE SOURCE: Dep. Chem., Univ. Illinois, Urbana, IL, 61801, USA
SOURCE: Journal of Organic Chemistry (1987), 52(26), 5742-5
CODEN: JOCEAH; ISSN: 0022-3263
DOCUMENT TYPE: Journal
LANGUAGE: English
CLASSIFICATION: 29-7 (Organometallic and Organometalloidal Compounds)
GRAPHIC IMAGE:

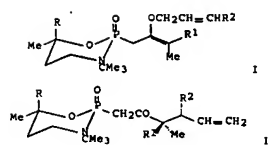
55

RX(2) OF 7 ...2 D ==> F



RX(2) RCT D 130826-97-0
RGT G 16940-66-2 NaBH4, H 7664-41-7 NH3
PRO F 130826-98-1
SOL 7732-18-5 Water

RX(3) OF 7 ...D ==> J



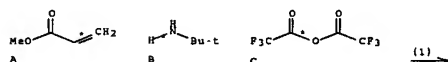
ABSTRACT:
The anions derived from allyl vinyl ethers I (R = Me; R1 = H, R2 = Me; R1 = R2 = H, Me) undergo rapid and highly selective Claisen rearrangements to give alkenyl ketone deriva. II. The degree of asym. induction is uniformly high (ca. 90:10) for various substituent patterns but depends markedly on the presence of lithium cations. The absolute sense of asym. induction has been established using chiral, nonracemic oxazaphosphorinane I (R = R2 = H). Two proposals for the transition structures of the phosphorus-stabilized anions are discussed.

SUPPL. TERM: Claisen rearrangement carbanion accelerated; asym induction Claisen rearrangement oxazaphosphorinane; allyl vinyl ether Claisen rearrangement; lithium cation asym Claisen rearrangement
INDEX TERM: Asymmetric synthesis and induction (in carbanion-accelerated Claisen rearrangement of allyl vinyl ethers via oxazaphosphorinanes)
INDEX TERM: Ethers, reactions
ROLE: RCT (Reactant); RACT (Reactant or reagent) (allyl vinyl, asym. carbanion-accelerated Claisen rearrangement of, via oxazaphosphorinane deriva.)
INDEX TERM: 96-33-3, Methyl 2-propenoate
ROLE: RCT (Reactant); RACT (Reactant or reagent) (addition of butylamine and sequential N-acylation of)
INDEX TERM: 504-61-0
ROLE: PROC (Process) (addition of, to allenylphosphoramidate)
INDEX TERM: 107-18-6, Allyl alcohol, reactions
ROLE: RCT (Reactant); RACT (Reactant or reagent) (addition of, to allenylphosphoramidate)
INDEX TERM: 7447-41-8, Lithium chloride, uses and miscellaneous
ROLE: USES (Uses) (asym. carbanion-accelerated Claisen rearrangement of oxazaphosphorinane derivative in presence of)
INDEX TERM: 111525-48-6P 111525-51-0P 111525-52-1P 111525-54-3P 111613-01-6P
ROLE: SPN (Synthetic preparation); PREP (Preparation) (asym. preparation of)
INDEX TERM: 141-97-9
ROLE: RCT (Reactant); RACT (Reactant or reagent) (enantioselective yeast reduction of)
INDEX TERM: 111525-47-4P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (preparation and addition reaction of, with allyl alc.)
INDEX TERM: 111525-43-6P

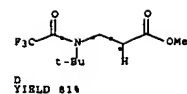
56

ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (preparation and addition reaction of, with hydroxybutene)
 INDEX TERM: 111525-42-9P
 ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (preparation and addition reactions of, with allylic alca.)
 INDEX TERM: 56816-01-4P
 ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (preparation and amidation of)
 INDEX TERM: 111525-44-1P 111525-45-2P 111525-46-3P 111525-48-5P 111612-96-5P
 ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (preparation and asym. carbanion accelerated Claisen rearrangement of)
 INDEX TERM: 111525-40-7P
 ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (preparation and borane reduction of)
 INDEX TERM: 111525-38-3P
 ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (preparation and reaction of, with Grignard reagent)
 INDEX TERM: 111525-41-8P
 ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (preparation and reaction of, with trichlorophosphine and hydroxybutyne, allenylphosphoramidates from)
 INDEX TERM: 111525-50-9P 111525-53-2P 111612-97-6P 111612-98-7P 111612-99-8P 111613-00-4P 111613-02-6P
 ROLE: SPN (Synthetic preparation); PREP (Preparation)
 (preparation of)
 INDEX TERM: 7719-12-2, Trichlorophosphine
 ROLE: RCT (Reactant); RACT (Reactant or reagent)
 (reaction of, with amino alca. and propargyl alca., allenylphosphoramidates from)
 INDEX TERM: 115-19-5
 ROLE: RCT (Reactant); RACT (Reactant or reagent)
 (reaction of, with trichlorophosphine and amino alca., allenylphosphoramidates from)
 INDEX TERM: 2028-63-9, 3-Hydroxy-1-butyne
 ROLE: RCT (Reactant); RACT (Reactant or reagent)
 (reaction of, with trichlorophosphine and amino alca., allenylphosphoramidates from)
 INDEX TERM: 111525-39-4
 ROLE: RCT (Reactant); RACT (Reactant or reagent)
 (reaction of, with trichlorophosphine and propargyl alca., allenylphosphoramidates from)

RX(1) OF 80 A + B + C ==> D...



57



RX(1) RCT A 96-33-3, B 75-64-9

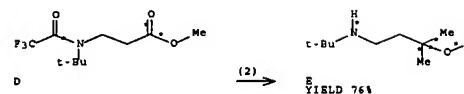
STAGE(1)

STAGE(2)

RCT C 407-25-0

PRO D 111525-38-3

RX(2) OF 80 ...D ==> E...



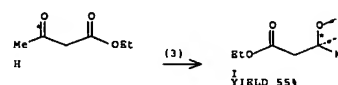
RX(2) RCT D 111525-38-3

RGT F 75-16-1 MeMgBr

PRO E 111525-39-4

SOL 60-29-7 Et2O

RX(3) OF 80 H ==> I...



RX(3) RCT H 141-97-9

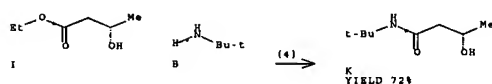
PRO I 56816-01-4

SOL 7732-18-5 Water

NTE yeast

58

RX(4) OF 80 ...I + B ==> K...

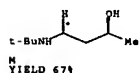
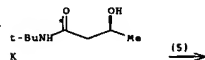


RX(4) RCT I 56816-01-4, B 75-64-9

RGT L 75-24-1 AlMe3

PRO K 111525-40-7

RX(5) OF 80 ...K ==> M...

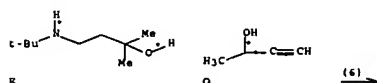


RX(5) RCT K 111525-40-7

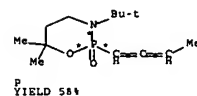
RGT N 14044-65-6 BH3-THF

PRO M 111525-41-8

RX(6) OF 80 ...E + O ==> P...



59

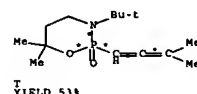
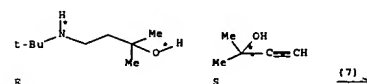


RX(6) RCT E 111525-39-4, O 2028-63-9

RGT Q 109-02-4 N-Methylmorpholine, R 7719-12-2 PC13

PRO P 111525-42-9

RX(7) OF 80 ...E + S ==> T...

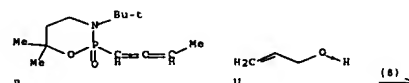


RX(7) RCT E 111525-39-4, S 115-19-5

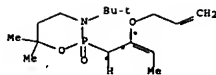
RGT Q 109-02-4 N-Methylmorpholine, R 7719-12-2 PC13

PRO T 111525-43-0

RX(8) OF 80 ...P + U ==> V...



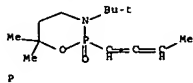
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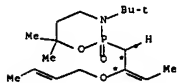
V
YIELD 64%

RX(8) RCT P 111525-42-9, U 107-18-6
RGT W 7646-69-7 NaH, X 75-65-0 t-BuOH
PRO V 111525-44-1
SOL 109-99-9 THF

RX(9) OF 80 ...P + Z ==> AA...



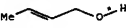
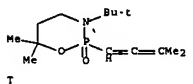
(9)



AA
YIELD 46%

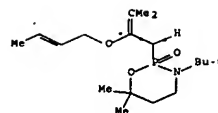
RX(9) RCT P 111525-42-9, Z 504-61-0
RGT W 7646-69-7 NaH, X 75-65-0 t-BuOH
PRO AA 111525-45-2
SOL 109-99-9 THF

RX(10) OF 80 ...T + Z ==> AB...



(10)

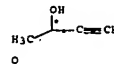
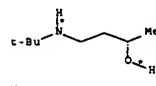
61



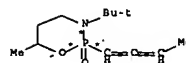
AB
YIELD 51%

RX(10) RCT T 111525-43-0, Z 504-61-0
RGT W 7646-69-7 NaH, X 75-65-0 t-BuOH
PRO AB 111525-46-3
SOL 109-99-9 THF

RX(11) OF 80 ...M + O ==> AC...



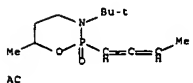
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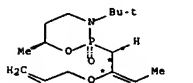
AC
YIELD 54%

RX(11) RCT M 111525-41-8, O 2028-63-9
RGT O 109-02-4 N-Methylmorpholine, R 7719-12-2 PC13
PRO AC 111525-47-4

RX(12) OF 80 ...AC + U ==> AD...



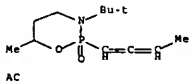
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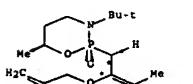
AD
YIELD 54%

RX(12) RCT AC 111525-47-4, U 107-18-6
RGT W 7646-69-7 NaH, X 75-65-0 t-BuOH
PRO AD 111525-48-5
SOL 109-99-9 THF

RX(13) OF 80 ...AC + U ==> AE...



(13)

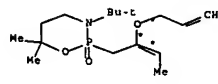


AE
YIELD 30%

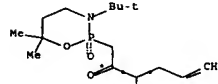
RX(13) RCT AC 111525-47-4, U 107-18-6
RGT W 7646-69-7 NaH, X 75-65-0 t-BuOH
PRO AE 111612-96-5
SOL 109-99-9 THF

63

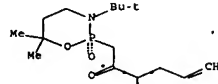
RX(14) OF 80 ...2 V ==> AF + AG



(14)



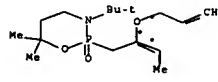
AF
YIELD 77%(52)



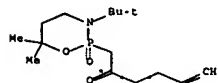
AG
YIELD 77%(48)

RX(14) RCT V 111525-44-1
RGT AH 7693-26-7 KH
PRO AF 111525-49-6, AG 111525-50-9
SOL 67-68-5 DMSO, 109-99-9 THF

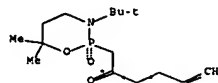
RX(15) OF 80 2 V ==> AF + AG



(15)



AF
YIELD 81%(91)

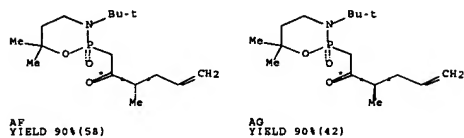
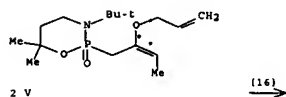


AG
YIELD 81%(9)

64

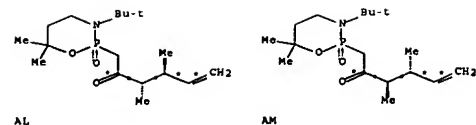
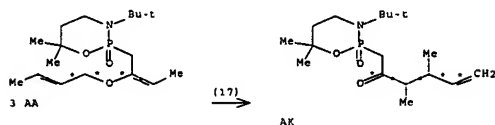
RX(15) RCT V 111525-44-1
RGT AH 7693-26-7 KH, AJ 7447-41-8 LiCl
PRO AF 111525-49-6, AG 111525-50-9
SOL 67-68-5 DMSO, 109-99-9 THF

RX(16) OF 80 2 V ==> AF + AG



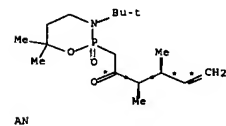
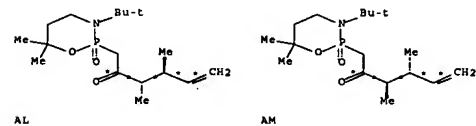
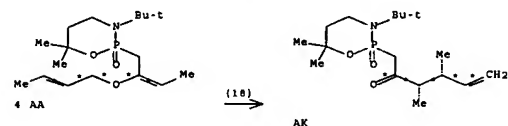
RX(16) RCT V 111525-44-1
PRO AF 111525-49-6, AG 111525-50-9
SOL 109-99-9 THF

RX(17) OF 80 ...3 AA ==> AK + AL + AM



RX(17) RCT AA 111525-45-2
RGT AH 7693-26-7 KH, AJ 7447-41-8 LiCl
PRO AK 111525-51-0, AL 111612-97-6, AM 111612-98-7
SOL 67-68-5 DMSO, 109-99-9 THF
NTE 80% overall

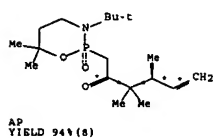
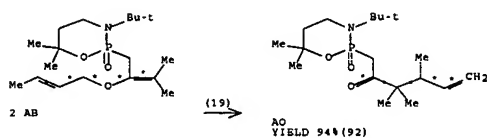
RX(18) OF 80 ...4 AA ==> AK + AL + AM + AN



65

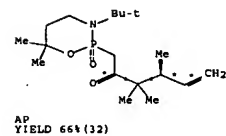
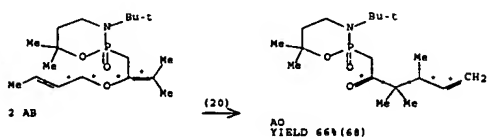
RX(18) RCT AA 111525-45-2
PRO AK 111525-51-0, AL 111612-97-6, AM 111612-98-7, AN 111612-99-8
SOL 109-99-9 THF
NTE 84% overall

RX(19) OF 80 ...2 AB ==> AO + AP



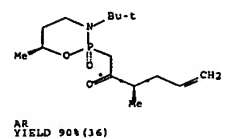
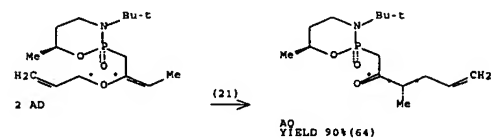
RX(19) RCT AB 111525-46-3
RGT AH 7693-26-7 KH, AJ 7447-41-8 LiCl
PRO AO 111525-52-1, AP 111525-53-2
SOL 67-68-5 DMSO, 109-99-9 THF

RX(20) OF 80 2 AB ==> AO + AP



RX(20) RCT AB 111525-46-3
PRO AO 111525-52-1, AP 111525-53-2
SOL 109-99-9 THF

RX(21) OF 80 ...2 AD ==> AQ + AR



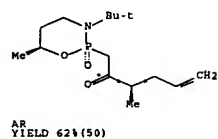
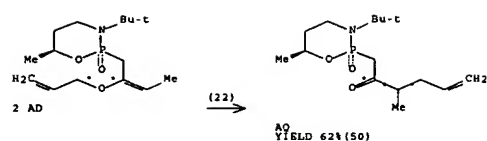
RX(21) RCT AD 111525-48-5
RGT AJ 7447-41-8 LiCl
PRO AQ 111525-54-3, AR 111613-00-4
SOL 109-99-9 THF

RX(22) OF 80 2 AD ==> AQ + AR

67

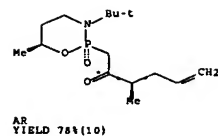
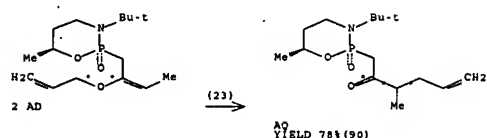
66

68



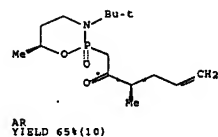
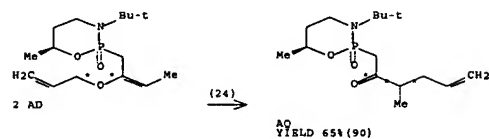
RX(22) RCT AD 111525-48-5
RGT AH 7693-26-7 KH
PRO AQ 111525-54-3, AR 111613-00-4
SOL 67-68-5 DMSO, 109-99-9 THF

RX(23) OF 80 2 AD ==> AQ + AR



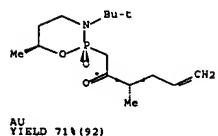
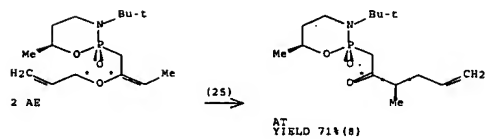
RX(23) RCT AD 111525-48-5
RGT AH 7693-26-7 KH, AJ 7447-41-8 LiCl
PRO AQ 111525-54-3, AR 111613-00-4
SOL 67-68-5 DMSO, 109-99-9 THF

RX(24) OF 80 2 AD ==> AQ + AR



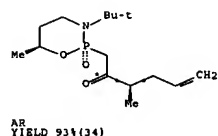
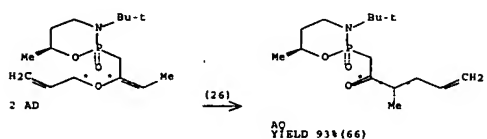
RX(24) RCT AD 111525-48-5
RGT AS 109-72-8 BuLi
PRO AQ 111525-54-3, AR 111613-00-4
SOL 67-68-5 DMSO, 109-99-9 THF

RX(25) OF 80 . . . 2 AE ###> AT + AU



RX(25) RCT AB 111612-96-5
RGT AH 7693-26-7 KH, AJ 7447-41-8 LiCl
PRO AT 111613-01-5, AU 111613-02-6
SOL 67-68-5 DMSO, 109-99-9 THF

RX(26) OF 80 2 AD ==> AQ + AR



RX(26) RCT AD 111525-48-5
PRO AQ 111525-54-3, AR 111613-00-4
SOL 109-99-9 THF

L27 ANSWER 6 OF 8 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 102:46134 CASREACT Full-text
TITLE: Herbicidal α -hydroxy phosphonates
INVENTOR(S): Gartner, Van R.
PATENT ASSIGNEE(S): Monsanto Co., USA
SOURCE: U.S., 9 pp. Division of U.S. 4,413,125.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
INT. PATENT CLASSIF.: A01N057-20
US PATENT CLASSIF.: 071086000
CLASSIFICATION: 21 (Organometallic and Organometalloidal Compounds)
Section cross-reference(s): 5
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

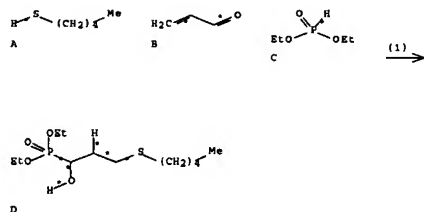
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4475943	A	19841009	US 1983-528700	19830901
US 4413125	A	19831101	US 1981-279371	19810701
PRIORITY APPLN. INFO.:			US 1981-279371	19810701

(R) (R) SOURCE(S): PARFAR 104766134
ABSTRACT:
(RO) (RIO) P(O) CR2 (OH) CHR3 CH4S [R, R1, alkyl, CH2PH; R2, R3, R4, R7 = H, alkenyl; R5 = piperidinyl, XR6, NR7R8; R6 = alkyl, alkenyl, aryl]; RS = alkyl, alkoxyalkyl;
X = S, O were prepared Thus Me(CH2)14SH was treated with H2C=CHCHO and (EtO)2PH to give 80% Me(CH2)4SCH2CH2CH(O)P(O)(OEt)2 (I). At 56.0 kg/ha, postemergent,
I gave complete control of Chenopodium album (lambsquarters).

SUPPL. TERM: hydroxy phosphonate herbicide prepn
INDEX TERM: Herbicides
(phosphonates, α -hydroxy)
INDEX TERM: 89222-47-9P 89222-48-0P 89222-49-1P 89222-50-4P
89222-51-5P 89222-52-6P 89222-53-7P 89222-54-8P
89222-55-9P 89222-56-0P 89222-57-1P 89222-59-3P
89222-60-6P 94128-48-0P
ROLE: AGR (Agricultural use); BAC (Biological activity or
effector, except adverse); BSU (Biological study,
unclassified); SPN (Synthetic preparation); BIOL (Biological
study); PRSP (Preparation); USSS (Uses)
(preparation and herbicidal activity of)

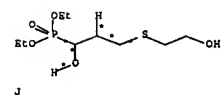
INDEX TERM: 89222-61-7P 89222-62-8P
 ROLE: SPN (Synthetic preparation); PREP (Preparation)
 (preparation of)
 INDEX TERM: 868-85-9
 ROLE: RCT (Reactant); RACT (Reactant or reagent)
 (reaction of, with acrolein)
 INDEX TERM: 762-04-9
 ROLE: RCT (Reactant); RACT (Reactant or reagent)
 (reaction of, with acrolein and amines or mercaptans)
 INDEX TERM: 60-24-2 74-85-1, reactions 75-33-2 75-64-9, reactions
 105-53-3 108-98-5, reactions 109-89-7, reactions
 110-66-7 110-89-4, reactions 111-92-2 594-39-8
 1639-09-4
 ROLE: RCT (Reactant); RACT (Reactant or reagent)
 (reaction of, with acrolein and di-Et phosphite)
 INDEX TERM: 17176-77-1
 ROLE: RCT (Reactant); RACT (Reactant or reagent)
 (reaction of, with acrolein and diethylamine)
 INDEX TERM: 107-03-9
 ROLE: RCT (Reactant); RACT (Reactant or reagent)
 (reaction of, with carbonyl compds. and di-Et phosphite)
 INDEX TERM: 107-02-8, reactions
 ROLE: RCT (Reactant); RACT (Reactant or reagent)
 (reaction of, with mercaptans or amines and di-Et
 phosphite)
 INDEX TERM: 78-85-3 78-94-4, reactions
 ROLE: RCT (Reactant); RACT (Reactant or reagent)
 (reaction of, with propanethiol and di-Et phosphite)

RX(1) OF 14 A + B + C ==> D



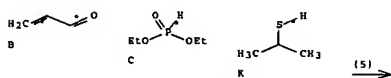
RX(1) RCT A 110-66-7, B 107-02-8, C 762-04-9
 PRO D 89222-47-9

RX(2) OF 14 B + C + E ==> F



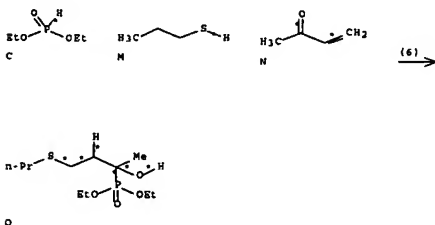
RX(4) RCT B 107-02-8, C 762-04-9, I 60-24-2
 PRO J 89222-50-4

RX(5) OF 14 B + C + K ==> L



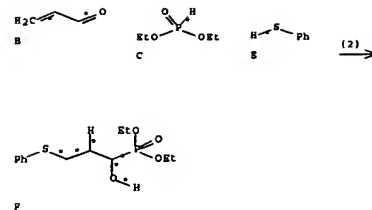
RX(5) RCT B 107-02-8, C 762-04-9, K 75-33-2
 PRO L 89222-51-5

RX(6) OF 14 C + M + N ==> O



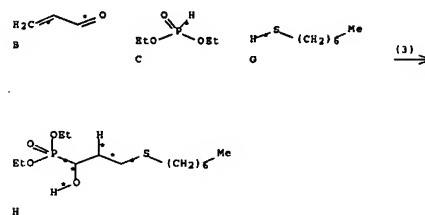
O

73



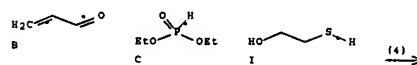
RX(2) RCT B 107-02-8, C 762-04-9, S 108-98-5
 PRO F 89222-48-0

RX(3) OF 14 B + C + G ==> H



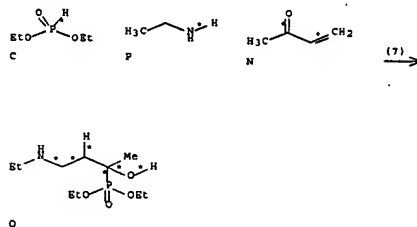
RX(3) RCT B 107-02-8, C 762-04-9, G 1639-09-4
 PRO H 89222-49-1

RX(4) OF 14 B + C + I ==> J



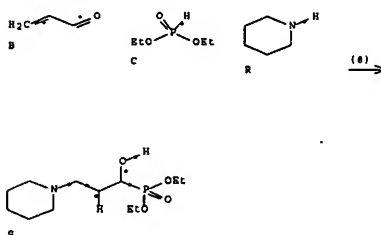
RX(6) RCT C 762-04-9, M 107-03-9, N 78-94-4
 PRO O 89222-53-7

RX(7) OF 14 C + P + N ==> Q



RX(7) RCT C 762-04-9, P 75-04-7, N 78-94-4
 PRO Q 89222-54-8

RX(8) OF 14 B + C + R ==> S

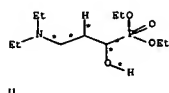
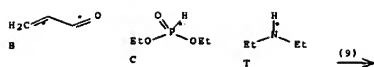


RX(8) RCT B 107-02-8, C 762-04-9, R 110-89-4
 PRO S 89222-55-9

RX(9) OF 14 B + C + T ==> U

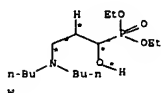
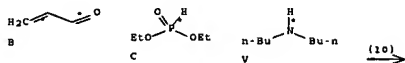
74

76



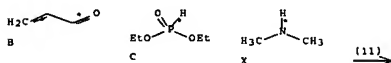
RX(9) RCT B 107-02-8, C 762-04-9, T 109-89-7
PRO U 89222-56-0

RX(10) OF 14 B + C + V ==> W

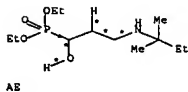
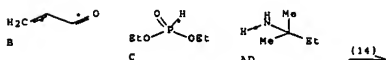


RX(10) RCT B 107-02-8, C 762-04-9, V 111-92-2
PRO W 89222-59-3

RX(11) OF 14 B + C + X ==> Y

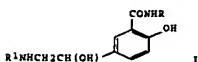


77

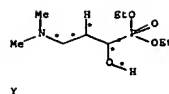


RX(14) RCT B 107-02-8, C 762-04-9, AD 594-39-8
PRO AE 89222-57-1

L27 ANSWER 7 OF 8 CASREACT COPYRIGHT 2007 ACS ON STN
ACCESSION NUMBER: 96:199236 CASREACT [Full-Text](#)
TITLE: Arylethanolamines derived from salicylamide with
alpha- and beta-adrenoceptor blocking activities.
Preparation of labetalol, its enantiomers and related
salicylamides
AUTHOR(S): Clifton, James S.; Collins, Ian; Hallett, Peter;
Hartley, David; Luntz, Lawrence H. C.; Wicks, Philip
D.
CORPORATE SOURCE: Chem. Dep., Glaxo Group Res. Ltd., Ware/Herts., SG12
0DJ, UK
SOURCE: Journal of Medicinal Chemistry (1982), 25(6), 670-9
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
CLASSIFICATION: 25-19 (Benzene, Its Derivatives, and Condensed
Benzenoid Compounds)
Section cross-reference(s): 1
GRAPHIC IMAGE:

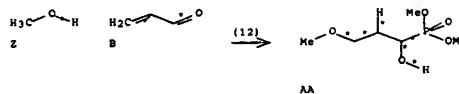


ABSTRACT:
Phenylethanolamines 1 (R = H, Me, PhCH2, HOCH2CH2, NH2; R1 = alkyl or
substituted alkyl) were prepared and shown to possess beta-adrenergic blocking
properties. When the basic N atom was substituted by some aralkyl groups, the
comps. also blocked alpha-adrenoceptors. Labetalol (1; R = H, R1 =
PhCH2CH2CHMe) is antihypertensive in animals and man, and syntheses of its 4



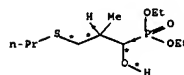
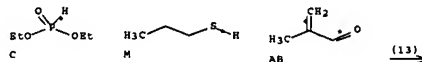
RX(11) RCT B 107-02-8, C 762-04-9, X 124-40-3
PRO Y 94128-48-0

RX(12) OF 14 Z + B ==> AA



RX(12) RCT Z 67-56-1, B 107-02-8
PRO AA 89222-62-8

RX(13) OF 14 C + M + AB ==> AC



RX(13) RCT C 762-04-9, M 107-03-9, AB 78-85-3
PRO AC 89222-52-6

RX(14) OF 14 B + C + AD ==> AE

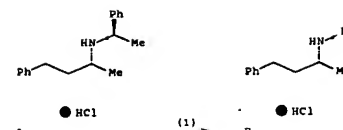
78

stereoisomers are described. The enantiomer with the (R) configuration at both
asym. centers possessed most of the beta-blocking activity but little
alpha-blocking activity. That with the (S) configuration at the alc. carbon
and the (R) configuration on the amino substituent is predominantly an
alpha-adrenoceptor blocking agent.

SUPPL. TERM: salicylamide ethanolamine deriv; labetalol stereoisomer
prepn antihypertensive
INDEX TERM: Antihypertensives
INDEX TERM: (labetalol enantiomers and related salicylamides as)
Isomerism and isomers
INDEX TERM: (of labetalol, antihypertensive activity and)
Molecular structure-biological activity relationship
(antihypertensive, of arylethanolamines derived from
salicylamide)
INDEX TERM: 24076-03-7 24076-19-5 81580-28-1
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(amidation of)
INDEX TERM: 24085-18-5
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(amidation of, or condensation with acetophenone and
formaldehyde)
INDEX TERM: 68164-04-5
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(amidation reaction, with (bromoacetyl)salicylamide)
INDEX TERM: 1611-38-7
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(catalytic hydrogenation of)
INDEX TERM: 104-53-0
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(condensation of, (aminohydroxyethyl)salicylamide)
INDEX TERM: 98-86-2, reactions
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(condensation of, with [(aminohydroxyethyl)amino]ethyl)s
alicylate and formaldehyde)
INDEX TERM: 22780-65-7
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(condensation of, with aldehydes and acetophenone)
INDEX TERM: 103-79-7
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(condensation of, with aminoacetophenone derivative)
INDEX TERM: 78-95-5
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(condensation of, with aniline derivative)
INDEX TERM: 2627-86-3 2886-69-9
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(condensation of, with benzylacetone)
INDEX TERM: 73866-23-6
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(condensation of, with benzylamine derivative, and amidation
of)
INDEX TERM: 2550-26-7
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(condensation of, with alpha-methylbenzylamine)
INDEX TERM: 75659-08-4P 81602-13-3P 81602-14-4P 81602-15-5P
ROLE: BAC (Biological activity or effector, except adverse);
BSU (Biological study, unclassified); SPN (Synthetic
preparation); TRU (Therapeutic use); BIOL (Biological
study); PREP (Preparation); USES (Uses)

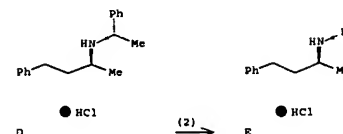
INDEX TERM: (preparation and antihypertensive activity of)
32780-63-5P 36256-61-8P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and catalytic hydrogenation of)
INDEX TERM: 80744-23-6P 81580-35-0P
ROLE: SPN (Synthetic preparation); PREP (Preparation)
(preparation and condensation with (bromoacetyl)salicylamide)
INDEX TERM: 81580-36-1P 81580-38-5P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and hydrogenation-benzoylation of)
INDEX TERM: 24076-04-8P 24076-14-0P 75615-55-3P 75615-56-4P
81580-32-7P 81580-33-8P 81580-37-2P 81580-06-0P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and hydrogenolysis of)
INDEX TERM: 72487-35-5P
ROLE: SPN (Synthetic preparation); PREP (Preparation)
(preparation and resolution of racemic)
INDEX TERM: 826-16-4P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and N-benzoylation of)
INDEX TERM: 24076-05-9P 24076-10-6P 24076-11-7P 24076-12-8P
24076-13-9P 24076-15-1P 24076-21-9P 24084-97-7P
25034-32-6P 32780-35-1P 32780-39-5P 32780-69-1P
32780-70-4P 32780-71-5P 32780-72-6P 32780-73-7P
36256-60-7P 36270-45-8P 54646-15-0P 56290-92-7P
63416-60-4P 63416-61-5P 63416-66-0P 64449-93-0P
64450-21-1P 64450-22-2P 64779-91-5P 64779-92-6P
64779-93-7P 70161-10-3P 72371-11-0P 75659-07-3P
81579-44-4P 81579-45-5P 81579-46-6P 81579-47-7P
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81579-57-9P 81579-58-0P 81579-59-1P 81579-60-4P
81580-04-3P 81580-05-4P 81580-06-5P 81580-07-6P
81580-08-7P 81580-09-8P 81580-10-1P 81580-11-2P
81580-12-3P 81580-13-4P 81580-14-5P 81580-15-6P
81580-16-7P 81580-17-8P 81580-18-9P 81580-19-0P
81580-20-3P 81580-21-4P 81580-22-5P 81580-23-6P
81580-24-7P 81580-25-8P 81580-26-9P 81580-27-0P
81580-29-2P 81580-30-5P 81580-31-6P 81580-34-9P
ROLE: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
INDEX TERM: 72487-34-4P
ROLE: SPN (Synthetic preparation); PREP (Preparation)
(preparation of enantiomeric components of racemic)
INDEX TERM: 459-59-6
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with chloropropanone)
INDEX TERM: 30566-92-8
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with phenylpropanone)

RX(1) OF 182 ...A ---> B...



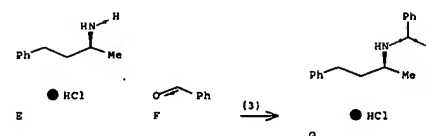
RX(1) RCT A 81580-32-7
PRO B 826-16-4
CAT 144-55-8 NaHCO₃

RX(2) OF 182 ...D ---> E...



RX(2) RCT D 81580-33-8
PRO E 81580-34-9
CAT 144-55-8 NaHCO₃

RX(3) OF 182 ...E + F ---> G...

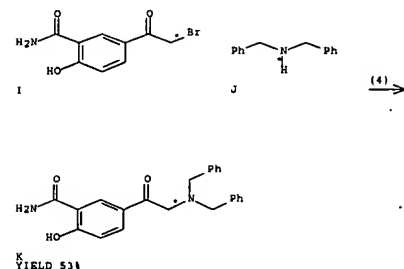


RX(3) RCT E 81580-34-9, F 100-52-7
RGT H 7647-01-0 HCl
PRO G 80744-23-6
CAT 144-55-8 NaHCO₃

81

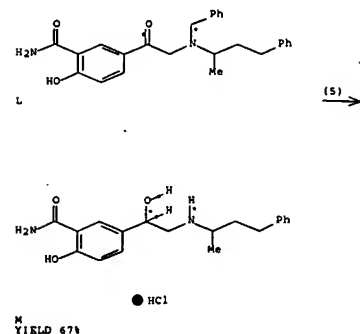
82

RX(4) OF 182 I + J ---> K...



RX(4) RCT I 73866-23-6, J 103-49-1
PRO K 30566-92-8

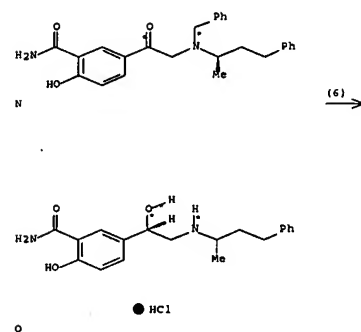
RX(5) OF 182 ...L ---> M



YIELD 67%

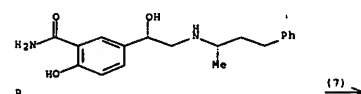
RX(5) RCT L 81579-50-2
RGT H 7647-01-0 HCl
PRO M 32780-64-6

RX(6) OF 182 ...N ---> O



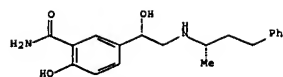
RX(6) RCT N 81580-36-1
PRO O 72487-34-4

RX(7) OF 182 ...P ---> Q



83

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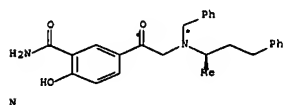


● HCl

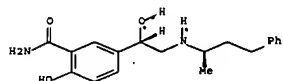
YIELD 87%

RX(7) RCT P 72487-32-2
RGT H 7647-01-0 HCl
PRO O 72487-34-4

RX(8) OF 182 ...N ==> Q



(8) →

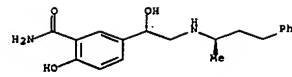


● HCl

Q

RX(8) RCT N 81580-36-1
PRO Q 72487-35-5

RX(9) OF 182 ...R ==> Q

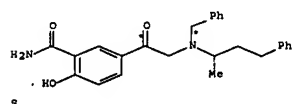


(9) →

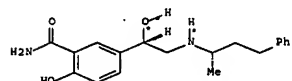
Q ● HCl

RX(9) RCT R 72487-31-1
RGT H 7647-01-0 HCl
PRO Q 72487-35-5

RX(10) OF 182 ...S ==> Q



(10) →



● HCl

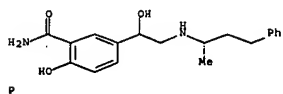
Q

85

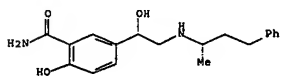
86

RX(10) RCT S 81580-38-3
PRO O 72487-34-4

RX(11) OF 182 P ==> O



(11) →

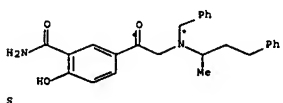


● HCl

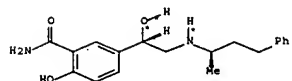
O

RX(11) RCT P 72487-32-2
RGT H 7647-01-0 HCl
PRO O 72487-34-4

RX(12) OF 182 ...S ==> Q



(12) →

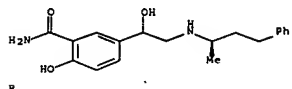


● HCl

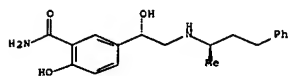
Q

RX(12) RCT S 81580-38-3
PRO Q 72487-35-5

RX(13) OF 182 R ==> Q



(13) →

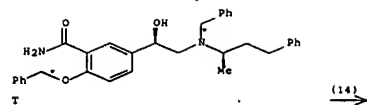


● HCl

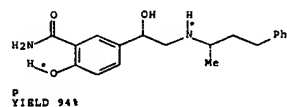
Q

RX(13) RCT R 72487-31-1
RGT H 7647-01-0 HCl
PRO Q 72487-35-5

RX(14) OF 182 T ==> P...

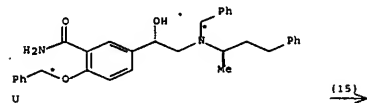


(14)

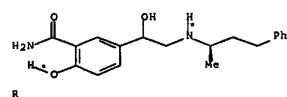


RX(14) RCT T 75615-55-3
PRO P 72487-32-2

RX(15) OF 182 U ==> R...

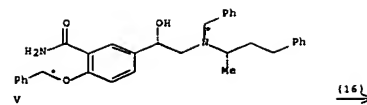


(15)

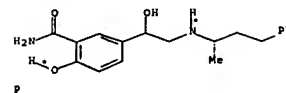


RX(15) RCT U 81580-37-2
PRO R 72487-31-1

RX(16) OF 182 V ==> P...

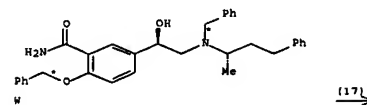


(16)

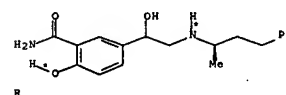


RX(16) RCT V 81585-06-0
PRO P 72487-32-2

RX(17) OF 182 W ==> R...

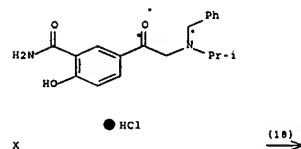


(17)

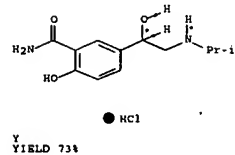


RX(17) RCT W 75615-56-4
PRO R 72487-31-1

RX(18) OF 182 ...X ==> Y

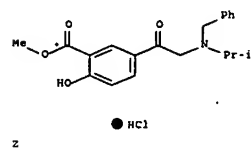


(18)

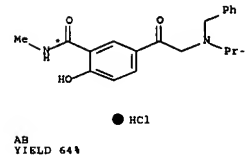


RX(18) RCT X 24076-04-8
PRO Y 24076-05-9

RX(19) OF 182 Z + AA ==> AB...

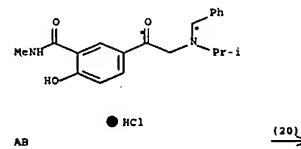


(19)

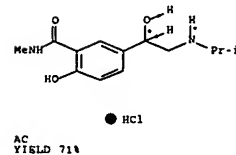


RX(19) RCT Z 24076-03-7, AA 74-89-5
PRO AB 24076-12-8

RX(20) OF 182 ...AB ==> AC

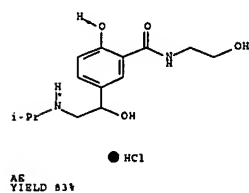
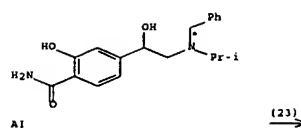
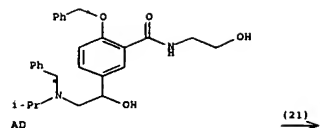


(20)



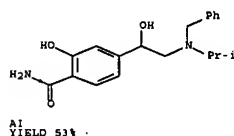
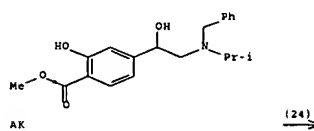
RX(20) RCT AB 24076-12-8
PRO AC 24076-13-9

RX(21) OF 182 ...AD ==> AE



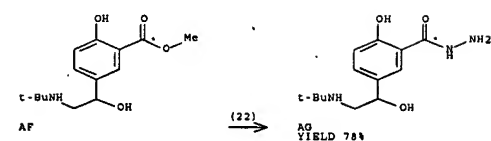
RX(23) RCT AI 24076-14-0
PRO AJ 24076-15-1

RX(24) OF 182 AK ==> AI...



RX(21) RCT AD 344754-55-8
RGT H 7647-01-0 HCl
PRO AS 24076-21-9

RX(22) OF 182 AF ==> AG



RX(22) RCT AF 27566-09-2
RGT AH 302-01-2 N2H4
PRO AG 24084-97-7

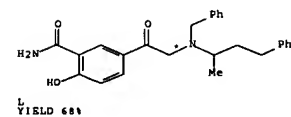
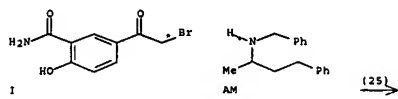
RX(23) OF 182 ...AI ==> AJ

93

94

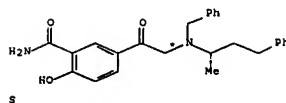
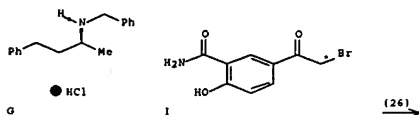
RX(24) RCT AK 81580-28-1
RGT AL 1336-21-6 NH4OH
PRO AI 24076-14-0

RX(25) OF 182 I + AM ==> L...



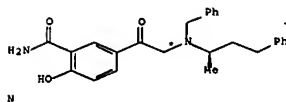
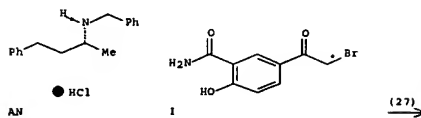
RX(25) RCT I 73866-23-6, AM 68164-04-5
PRO L 81579-50-2

RX(26) OF 182 ...G + I ==> S...



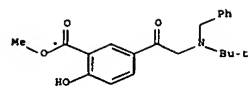
RX(26) RCT G 80744-23-6, I 73866-23-6
PRO S 81580-38-3
CAT 144-55-8 NaHCO3

RX(27) OF 182 ...AN + I ==> N...



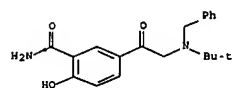
RX(27) RCT AN 81580-35-0, I 73866-23-6
PRO N 81580-36-1
CAT 144-55-8 NaHCO3

RX(28) OF 182 AO ==> AP...



● HCl

AO (28)

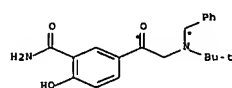


● HCl

AP YIELD 80%

RX(28) RCT AO 27475-26-9
 RCT AL 1336-21-6 NH4OH
 PRO AP 36270-45-8

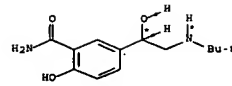
RX(29) OF 182 ...AP ==> AQ



● HCl

AP (29)

97

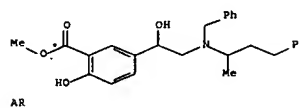


● HCl

AQ YIELD 75%

RX(29) RCT AP 36270-45-8
 PRO AQ 24076-10-6

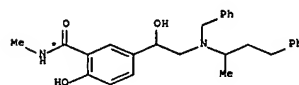
RX(30) OF 182 AR + AA ==> AS...



(30)

AR

AA



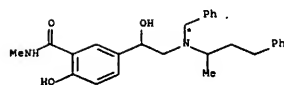
● HCl

AS

RX(30) RCT AR 345948-53-0, AA 74-89-5
 PRO AS 81579-51-3

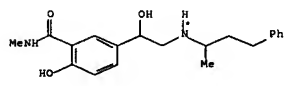
RX(31) OF 182 ...AS ==> AT

98



● HCl

AS (31)



● HCl

AT YIELD 28%

RX(31) RCT AS 81579-51-3
 PRO AT 81580-27-0

RX(32) OF 182 AU ==> AV...



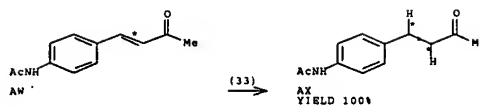
(32)

AV YIELD 76%

RX(32) RCT AU 1611-38-7
 PRO AV 63416-61-5

RX(33) OF 182 AW ==> AX...

99

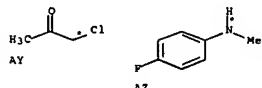


(33)

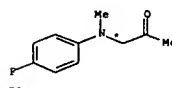
AX YIELD 100%

RX(33) RCT AW 27861-32-1
 PRO AX 54646-15-0

RX(34) OF 182 AY + AZ ==> BA...



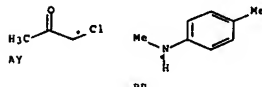
(34)



BA

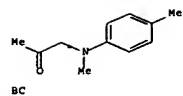
RX(34) RCT AY 78-95-5, AZ 459-59-6
 PRO BA 64450-21-1
 CAT 144-55-8 NaHCO3

RX(35) OF 182 AY + BB ==> BC...



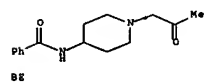
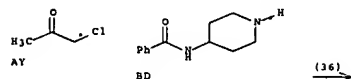
(35)

100



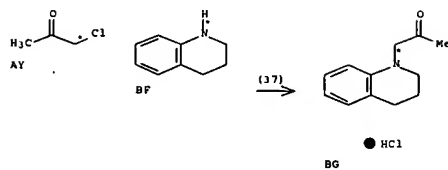
RX(35) RCT AY 78-95-5, BB 623-08-5
PRO BC 64450-22-2
CAT 144-55-8 NaHCO3

RX(36) OF 182 AY + BD ==> BE...



RX(36) RCT AY 78-95-5, BD 33953-37-6
PRO BE 81580-30-5
CAT 144-55-8 NaHCO3

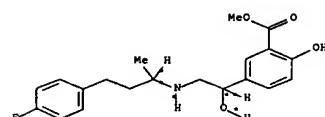
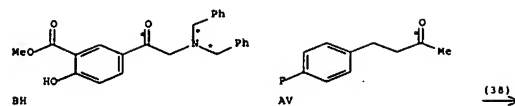
RX(37) OF 182 AY + BF ==> BG...



RX(37) RCT AY 78-95-5, BF 635-46-1

PRO BG 81580-31-6
CAT 144-55-B NaHCO3

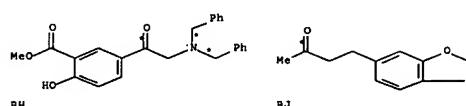
RX(38) OF 182 ...BH + AV ==> BI...



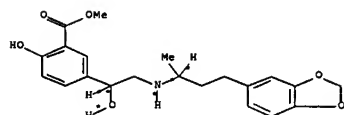
BI
YIELD 75%

RX(38) RCT BH 36270-04-9, AV 63416-61-5
RGT H 7647-01-0 HCl
PRO BI 63416-60-4

RX(39) OF 182 BH + BJ ==> BK...

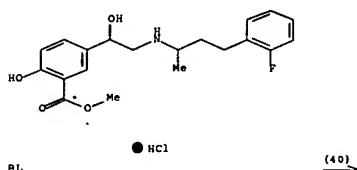


(39)

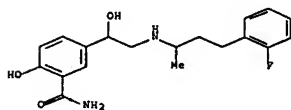
BK
YIELD 934

RX(39) RCT BH 36270-04-9, BJ 55418-52-5
RGT H 7647-01-0 HCl
PRO BK 56290-92-7

RX(40) OF 182 ...BL ==> BM

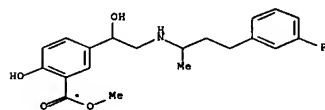


BL

BM
YIELD 329

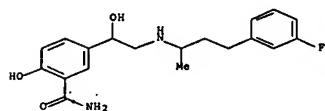
RX(40) RCT BL 63416-66-0
RGT AL 1336-21-6 NH4OH
PRO BM 64779-92-6

RX(41) OF 182 BN ==> BO



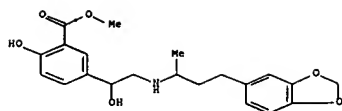
BN ● HCl

(41)

BO
YIELD 394

RX(41) RCT BN 63416-63-7
RGT AL 1336-21-6 NH4OH
PRO BO 81580-09-8

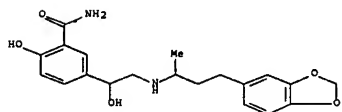
RX(42) OF 182 ...BK ==> BP



● HCl

(42)

BK

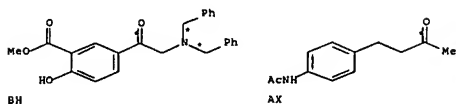


● HCl

BP
YIELD 81%

RX(42) RCT BK 56290-92-7
RGT H 7647-01-0 HCl, AL 1336-21-6 NH4OH
PRO BP 70161-10-3

RX(43) OF 182 ...BH + AX ==> BQ...



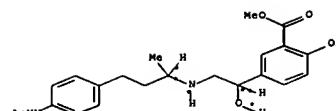
BH

AcNH

AX

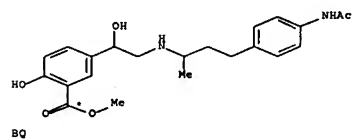
(43)

105

AcNH
BQ
YIELD 51%

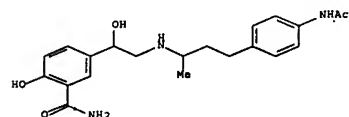
RX(43) RCT BH 36270-04-9, AX 54646-15-0
PRO BQ 81579-44-4

RX(44) OF 182 ...BQ ==> BR



BQ

(44)



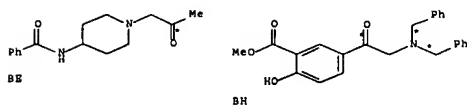
● HCl

BR
YIELD 94%

RX(44) RCT BQ 81579-44-4
RGT H 7647-01-0 HCl, AL 1336-21-6 NH4OH
PRO BR 81580-14-5

RX(45) OF 182 ...BE + BH ==> BS...

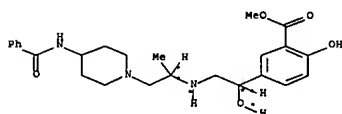
106



BE

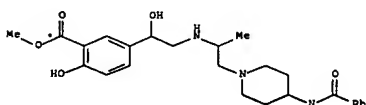
BH

(45)

BS
YIELD 51%

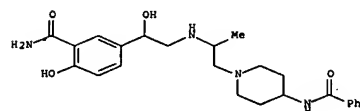
RX(45) RCT BS 81580-30-5, BH 36270-04-9
PRO BS 81579-48-8

RX(46) OF 182 ...BS ==> BT



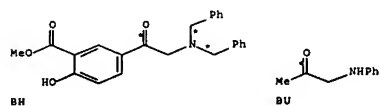
BS

(46)

BT
YIELD 86%

RX(46) RCT BS 81579-48-8
RGT AL 1336-21-6 NH4OH
PRO BT 81579-57-9

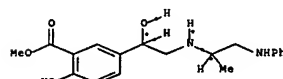
RX(47) OF 182 BH + BU ==> BV...



BH

BU

(47)



● 2 HCl

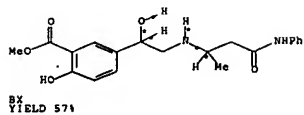
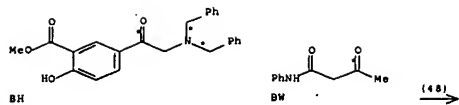
BV
YIELD 84%

RX(47) RCT BH 36270-04-9, BU 4504-29-4
RGT H 7647-01-0 HCl
PRO BV 81579-49-9

RX(48) OF 182 BH + BW ==> BX...

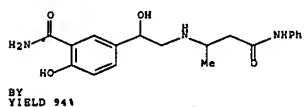
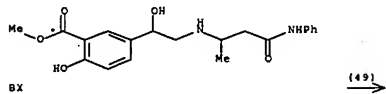
107

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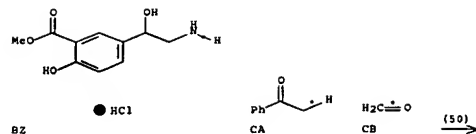
RX(48) RCT BH 36270-04-9, BW 102-01-2
PRO BX 64449-93-0

RX(49) OF 182 ...BX ==> BY



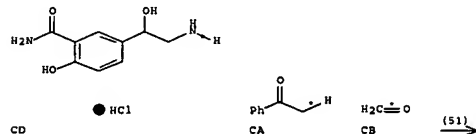
RX(49) RCT BX 64449-93-0
RGT AL 1336-21-6 NH4OH
PRO BY 81580-25-8

RX(50) OF 182 BZ + CA + CB ==> CC...



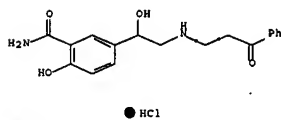
RX(50) RCT BZ 24085-18-5, CA 98-86-2, CB 50-00-0
PRO CC 81579-45-5

RX(51) OF 182 ...CD + CA + CB ==> CE



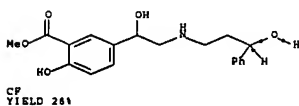
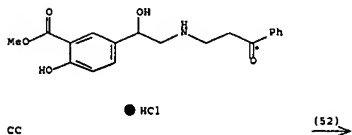
109

110



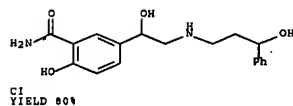
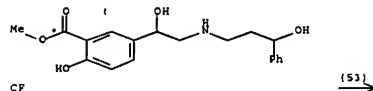
RX(51) RCT CD 32780-65-7, CA 98-86-2, CB 50-00-0
PRO CE 81580-18-9

RX(52) OF 182 ...CC ==> CF...



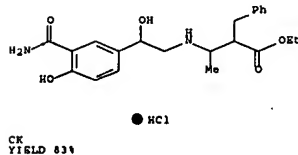
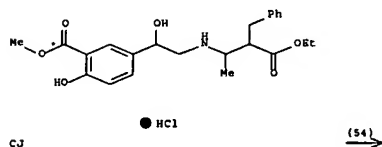
RX(52) RCT CC 81579-45-5
RGT CG 16949-15-8 LiBH4
PRO CF 81579-46-6
CAT 16940-66-2 NaBH4

RX(53) OF 182 ...CF ==> CI



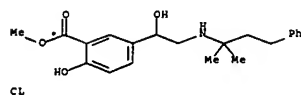
RX(53) RCT CF 81579-46-6
RGT AL 1336-21-6 NH4OH
PRO CI 81579-59-1

RX(54) OF 182 CJ ==> CK

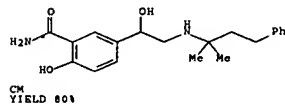


RX(54) RCT CJ 81579-47-7
RGT AL 1336-21-6 NH4OH
PRO CK 81579-58-0

RX(55) OF 182 CL ==> CM

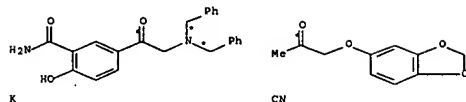


(55)

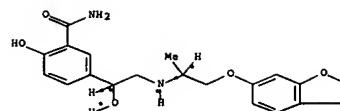


RX(55) RCT CL 345651-86-7
RGT AL 1336-21-6 NH4OH
PRO CM 32780-39-5

RX(56) OF 182 ...K + CN ==> CO

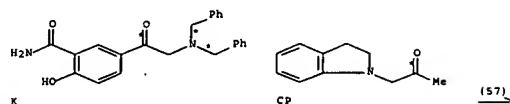


(56)

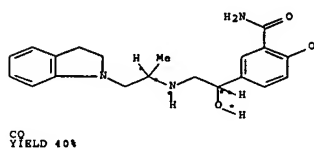


RX(56) RCT K 30566-92-8, CN 99807-06-4
PRO CO 81580-20-3

RX(57) OF 182 ...K + CP ==> CQ



(57)

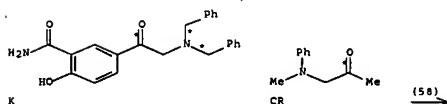


RX(57) RCT K 30566-92-8, CP 344304-70-7
PRO CQ 81579-55-7

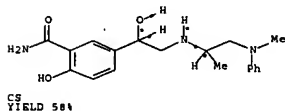
RX(58) OF 182 ...K + CR ==> CS

113

114

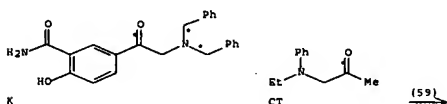


(58)

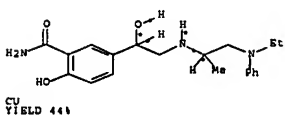


RX(58) RCT K 30566-92-8, CR 15885-06-0
PRO CS 72371-11-0

RX(59) OF 182 ...K + CT ==> CU

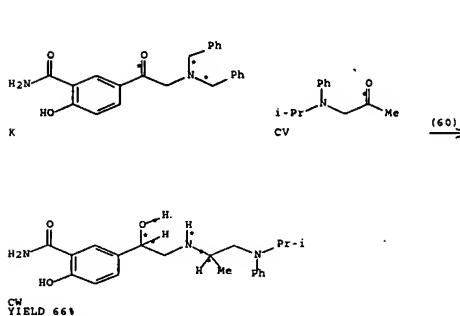


(59)



RX(59) RCT K 30566-92-8, CT 31199-19-6
PRO CU 81580-04-3

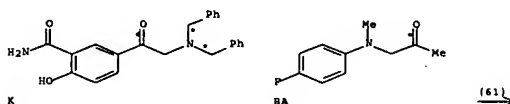
RX(60) OF 182 ...K + CV ==> CW



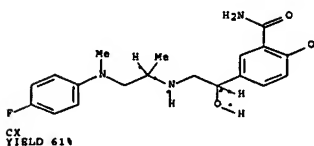
(60)

RX(60) RCT K 30566-92-8, CV 344308-74-3
PRO CW 81580-05-4

RX(61) OF 182 ...K + BA ==> CX



(61)

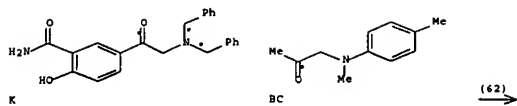


RX(61) RCT K 30566-92-8, BA 64450-21-1

115

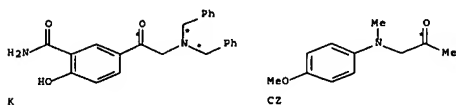
116

RX(62) OF 182 ...K + BC ==> CY



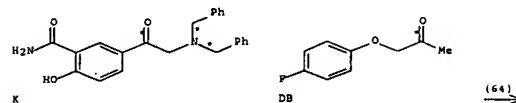
RX(62) RCT K 30566-92-8, BC 64450-22-2
PRO CY 81580-21-4

RX(63) OF 182 ...K + CZ ==> DA



RX(63) RCT K 30566-92-8, CZ 64450-19-7
PRO DA 81580-24-7

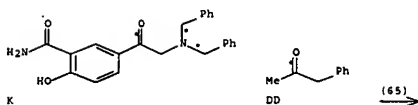
RX(64) OF 182 ...K + DB ==> DC



RX(64) RCT K 30566-92-8, DB 81580-29-2
RGT H 7647-01-0 HCl
PRO DC 81580-19-0

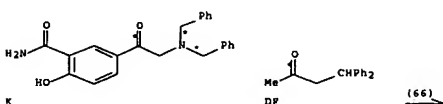
RX(64) RCT K 30566-92-8, DB 81580-29-2
RGT H 7647-01-0 HCl
PRO DC 81580-19-0

RX(65) OF 182 ...K + DD ==> DE



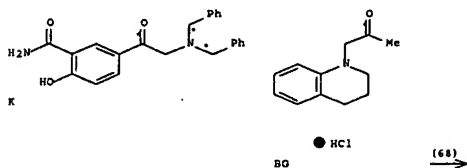
RX(65) RCT K 30566-92-8, DD 103-79-7
RGT H 7647-01-0 HCl
PRO DE 81579-52-4

RX(66) OF 182 ...K + DF ==> DG



RX(66) RCT K 30566-92-8, DF 64450-18-6
RGT H 7647-01-0 HCl
PRO DI 81580-06-5

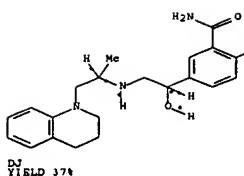
RX(67) OF 182 ...K + BG ==> DJ



RX(67) RCT K 30566-92-8, BG 64450-18-6
RGT H 7647-01-0 HCl
PRO DI 81580-06-5

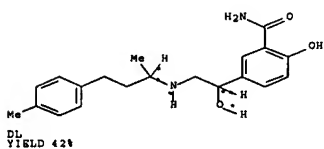
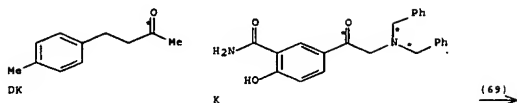
RX(68) OF 182 ...K + BG ==> DJ





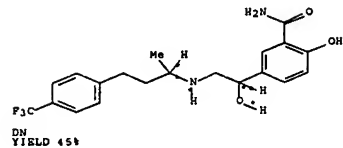
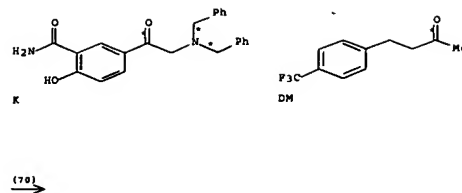
RX(68) RCT K 30566-92-8, BG 81580-31-6
PRO DJ 81579-56-8

RX(69) OF 182 ...DK + K ==> DL



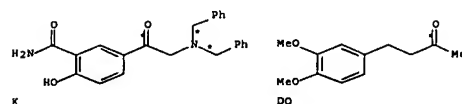
RX(69) RCT DK 7774-79-0, K 30566-92-8
PRO DL 81580-07-6

RX(70) OF 182 ...K + DM ==> DN



RX(70) RCT K 30566-92-8, DM 57132-19-1
PRO DN 81580-08-7

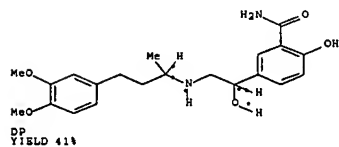
RX(71) OF 182 ...K + DO ==> DP



(71)

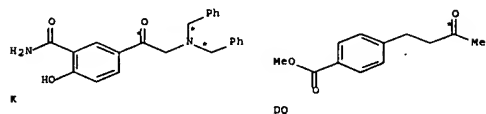
121

122

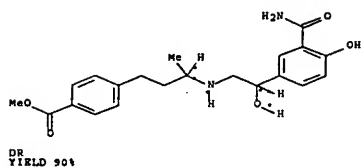


RX(71) RCT K 30566-92-8, DO 6302-60-9
PRO DP 81580-10-1

RX(72) OF 182 ...K + DQ ==> DR...

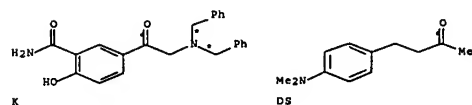


(72)

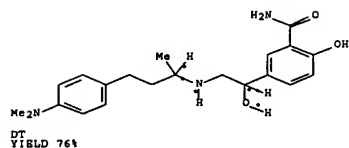


RX(72) RCT K 30566-92-8, DO 74248-99-0
PRO DR 81580-11-2

RX(73) OF 182 ...K + DS ==> DT

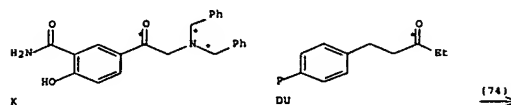


(73)



RX(73) RCT K 30566-92-8, DS 30780-30-4
PRO DT 81580-13-4

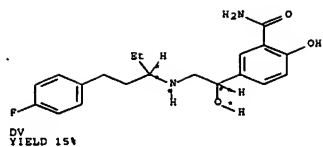
RX(74) OF 182 ...K + DU ==> DV



(74)

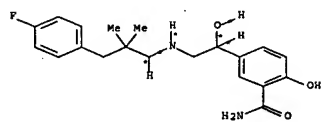
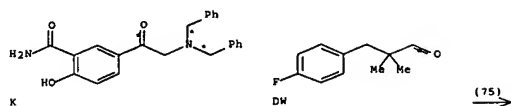
123

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RX(74) RCT K 30566-92-8, DU 63416-75-1
PRO DV 81580-16-7

RX(75) OF 182 ...K + DW ==> DX

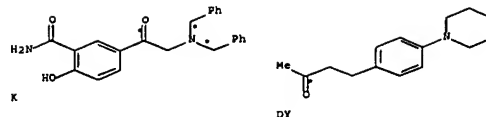


● HCl

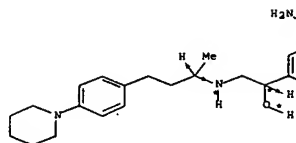
DX
YIELD 42%

RX(75) RCT K 30566-92-8, DW 4092-92-6
RGT H 7647-01-0 HCl
PRO DX 81580-17-8

RX(76) OF 182 ...K + DY ==> DZ



(76)

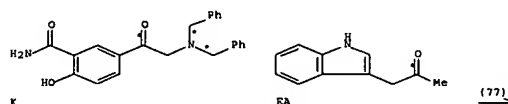


● HCl

DZ
YIELD 27%

RX(76) RCT K 30566-92-8, DY 344304-03-6
RGT H 7647-01-0 HCl
PRO DZ 81580-15-6

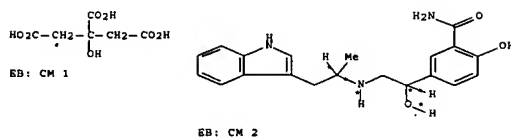
RX(77) OF 182 ...K + EA ==> EB



(77)

125

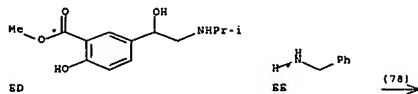
126



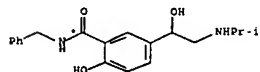
EB: CM 2

RX(77) RCT K 30566-92-8, EA 1201-26-9
PRO EB 81579-54-6
CAT 77-92-9 Citric acid

RX(78) OF 182 ED + EE ==> EF



(78)

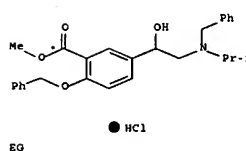


● HCl

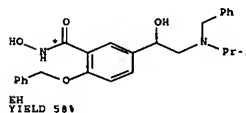
EF

RX(78) RCT ED 36270-12-9, EE 100-46-9
PRO EF 24076-11-7

RX(79) OF 182 EG ==> EH...

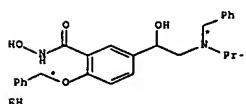


(79)

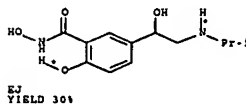


RX(79) RCT EG 24076-19-5
RGT EI 7803-49-8 NH2OH
PRO EH 36256-61-8

RX(80) OF 182 ...EH ==> EJ



(80)



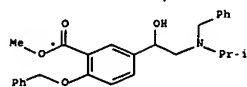
RX(80) RCT EH 36256-61-8

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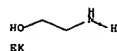
PRO EJ 36256-60-7

RX(81) OF 182 EG + EK ==> AD...



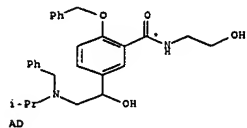
● HCl

EG



EK

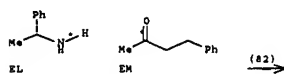
(81)



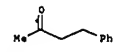
AD

RX(81) RCT EG 24076-19-5, EK 141-43-5
PRO AD 344754-55-8

RX(82) OF 182 EL + EM ==> A...



EL



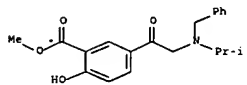
EM

(82)

129

PRO AN 81580-35-0
CAT 144-55-8 NaHCO₃

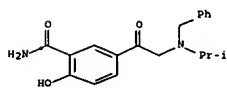
RX(85) OF 182 Z ==> X...



● HCl

Z

(85)

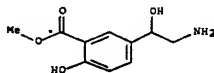


● HCl

X
YIELD 77%

RX(85) RCT Z 24076-03-7
RGT AL 1336-21-6 NH₄OH
PRO X 24076-04-8

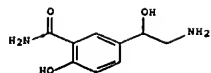
RX(86) OF 182 BZ ==> CD...



● HCl

BZ

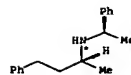
(86)



● HCl

CD
YIELD 62%

131

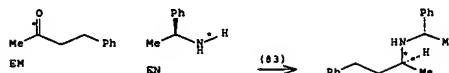


● HCl

A
YIELD 37%

RX(82) RCT EL 3886-69-9, EM 2550-26-7
RGT H 7647-01-0 HCl
PRO A 81580-32-7

RX(83) OF 182 EM + EN ==> D...

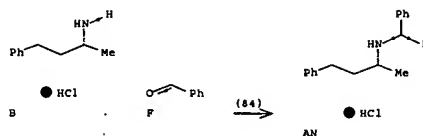


● HCl

D
YIELD 43%

RX(83) RCT EM 2550-26-7, EN 2627-86-3
RGT H 7647-01-0 HCl
PRO D 81580-33-8

RX(84) OF 182 ...B + F ==> AN...



● HCl

B

F

(84)

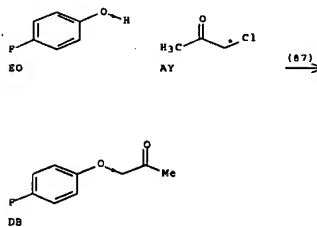
AN

RX(84) RCT B 826-16-4, F 100-52-7
RGT H 7647-01-0 HCl

130

RX(86) RCT BZ 24085-18-5
RGT AL 1336-21-6 NH₄OH
PRO CD 32780-65-7

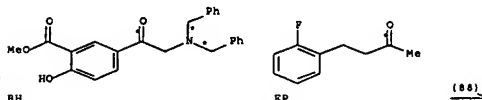
RX(87) OF 182 EO + AY ==> DB...



DB

RX(87) RCT EO 371-41-5, AY 78-95-5
PRO DB 81580-29-2
CAT 144-55-8 NaHCO₃

RX(88) OF 182 BH + EP ==> BL...

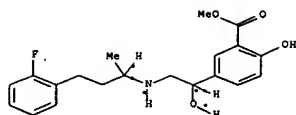


BH

EP

(88)

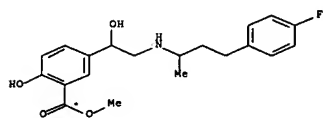
132



BL
YIELD 76%

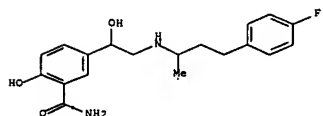
RX(88) RCT BH 36270-04-9, EP 63416-65-9
RGT H 7647-01-0 HCl
PRO BL 63416-66-0

RX(89) OF 182 ...BI ==> EQ



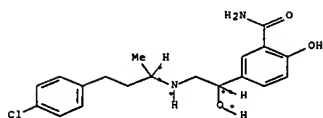
BI

(89)



EQ
YIELD 90%

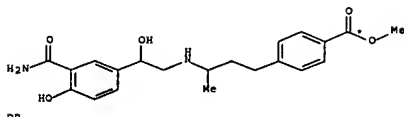
133



ET
YIELD 13%

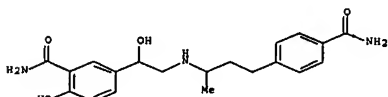
RX(91) RCT K 30566-92-8, ES 3506-75-0
RGT H 7647-01-0 HCl
PRO ET 64779-93-7

RX(92) OF 182 ...DR ==> EU



DR

(92)



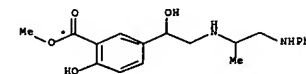
EU
YIELD 41%

RX(92) RCT DR 81580-11-2
RGT H 7647-01-0 HCl, AL 1336-21-6 NH4OH
PRO EU 81580-12-3

135

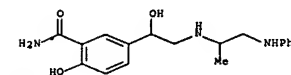
RX(89) RCT BI 63416-60-4
RGT H 7647-01-0 HCl, AL 1336-21-6 NH4OH
PRO EQ 64779-91-5

RX(90) OF 182 ...BV ==> BR



BV

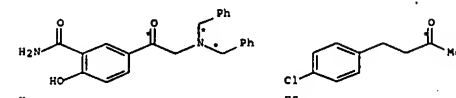
(90)



BR
YIELD 30%

RX(90) RCT BV 81579-49-9
RGT AL 1336-21-6 NH4OH
PRO BR 81579-60-4

RX(91) OF 182 ...K + ES ==> ET



K

(91)

134

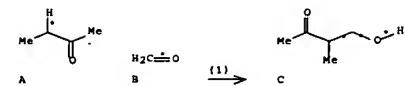
L27 ANSWER 8 OF 8 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 95:61370 CASREACT Full-text
TITLE: Synthesis of substituted 3-amino alcohols by reduction
of oximes of β -keto alcohols
AUTHOR(S): Latypova, F. N.; Malina, Yu. F.; Unkovskii, B. V.
CORPORATE SOURCE: USSR
SOURCE: Khimiya i Tekhnologiya Organicheskikh Proizvodstv
(1979), 9(2), 3-8
CODEN: KTPOPN
DOCUMENT TYPE: Journal
LANGUAGE: Russian
CLASSIFICATION: 23-7 (Aliphatic Compounds)
Section cross-reference(s): 25

ABSTRACT:
Condensation reaction of HCHO with PhCOEt and MeOH containing KOH yielded 80% HOCH₂CHMeCOPh (I). Oximation of HOCRR1CHR2COR3 (R = R1 = R3 = Me, R2 = H; R = R1 = H, R2 = R3 = Me; R = H, R1 = R2 = R3 = Me) and I gave 65-85% yield of the corresponding HOCRR1CHR2CR3:NOH, which were reduced with Raney Ni and with LiAlH₄ to give 50-70% and 35-50% HOCRR1CHR2CHR3NH₂ (same R-R3), resp.

SUPPL. TERM: amino alc; oxime hydroxy ketone redn
INDEX TERM: Oximes
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(of β -hydroxy ketones, preparation and reduction of,
 β -amino alcs. by)
INDEX TERM: Ketones, reactions
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(oximation of)
INDEX TERM: Alcohols, preparation
ROLE: SPN (Synthetic preparation); PREP (Preparation)
(amino, β -, preparation of, by reduction of oximes of
 β -hydroxy ketones)
INDEX TERM: 93-55-0
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(condensation reaction of, with formaldehyde)
INDEX TERM: 50-00-0, reactions
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(condensation reaction of, with propiophenone)
INDEX TERM: 123-42-2 565-79-7 3393-64-4
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(oximation of)
INDEX TERM: 16735-22-1P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP
(Preparation); RACT (Reactant or reagent)
(preparation and oximation of)
INDEX TERM: 17918-67-1P 69125-01-5P 78401-96-4P 78401-97-5P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP
(Preparation); RACT (Reactant or reagent)
(preparation and reduction of, β -amino alc. by)
INDEX TERM: 70772-78-0P 78401-94-2P 78401-95-3P 78420-43-6P
ROLE: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

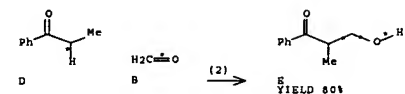
RX(1) OF 66 A + B ==> C...

136



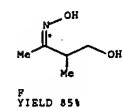
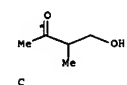
RX(1) RCT A 78-93-3, B 50-00-0
PRO C 3393-64-4

RX(2) OF 66 D + B ==> E...



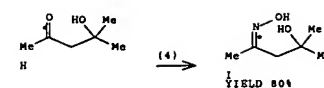
RX(2) RCT D 93-55-0, B 50-00-0
PRO E 16735-22-1

RX(3) OF 66 ...C ==> F...



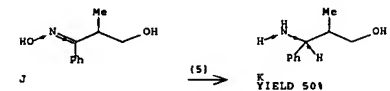
RX(3) RCT C 3393-64-4
RGT G 7803-49-8 NH2OH
PRO F 69125-01-5

RX(4) OF 66 H ==> I...



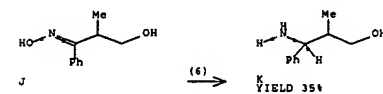
RX(4) RCT H 123-42-2
RGT G 7803-49-8 NH2OH
PRO I 17918-67-1

RX(5) OF 66 ...J ==> K



RX(5) RCT J 78401-97-5
PRO K 78401-95-3

RX(6) OF 66 J ==> K

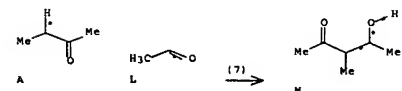


RX(6) RCT J 78401-97-5
PRO K 78401-95-3

RX(7) OF 66 A + L ==> M...

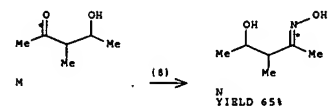
137

138



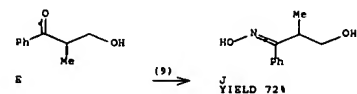
RX(7) RCT A 78-93-3, L 75-07-0
PRO M 565-79-7

RX(8) OF 66 ...M ==> N...



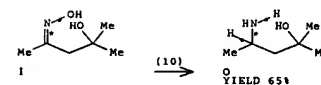
RX(8) RCT M 565-79-7
RGT G 7803-49-8 NH2OH
PRO N 78401-96-4

RX(9) OF 66 ...E ==> J...



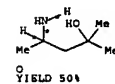
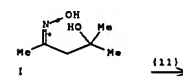
RX(9) RCT E 16735-22-1
RGT G 7803-49-8 NH2OH
PRO J 78401-97-5

RX(10) OF 66 ...I ==> O



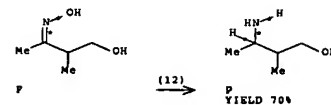
RX(10) RCT I 17918-67-1
PRO O 70772-78-0

RX(11) OF 66 I ==> O



RX(11) RCT I 17918-67-1
PRO O 70772-78-0

RX(12) OF 66 ...F ==> P

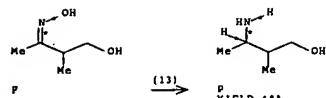


RX(12) RCT P 69125-01-5
PRO P 78401-94-2

RX(13) OF 66 P ==> P

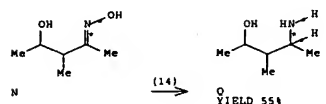
139

140



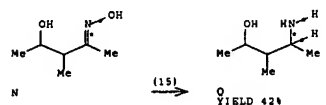
RX(13) RCT F 69125-01-5
PRO P 78401-94-2

RX(14) OF 66 ...N ==> Q



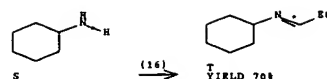
RX(14) RCT N 78401-96-4
PRO Q 78420-43-6

RX(15) OF 66 N ==> Q



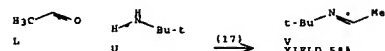
RX(15) RCT N 78401-96-4
PRO Q 78420-43-6

RX(16) OF 66 R + S ==> T...



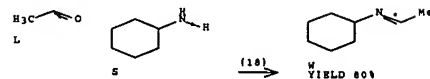
RX(16) RCT R 123-38-6, S 108-91-8
PRO T 1195-49-9

RX(17) OF 66 L + U ==> V...



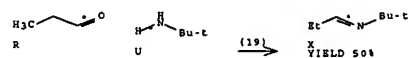
RX(17) RCT L 75-07-0, U 75-64-9
PRO V 7020-80-6

RX(18) OF 66 L + S ==> W...



RX(18) RCT L 75-07-0, S 108-91-8
PRO W 1193-93-7

RX(19) OF 66 R + U ==> X...

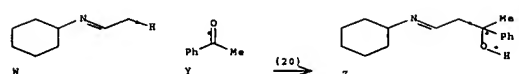


RX(19) RCT R 123-38-6, U 75-64-9
PRO X 7020-81-7

RX(20) OF 66 ...W + Y ==> Z...

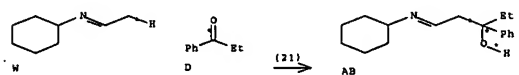
141

142



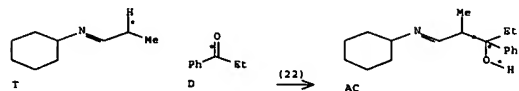
RX(20) RCT W 1193-93-7, Y 98-86-2
PRO Z 1217-04-5
CAT 816-43-3 LInEt2

RX(21) OF 66 ...W + D ==> AB...



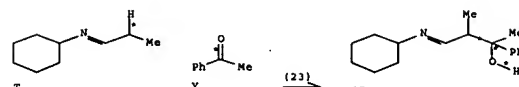
RX(21) RCT W 1193-93-7, D 93-55-0
PRO AB 343617-82-3
CAT 816-43-3 LInEt2

RX(22) OF 66 ...T + D ==> AC...



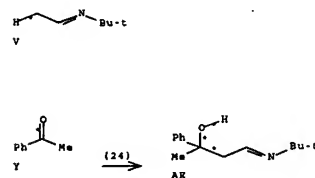
RX(22) RCT T 1195-49-9, D 93-55-0
PRO AC 343623-11-0
CAT 816-43-3 LInEt2

RX(23) OF 66 ...T + Y ==> AD...



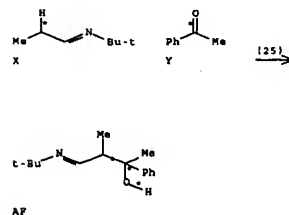
RX(23) RCT T 1195-49-9, Y 98-86-2
PRO AD 1712-88-5
CAT 816-43-3 LInEt2

RX(24) OF 66 ...V + Y ==> AE...



RX(24) RCT V 7020-80-6, Y 98-86-2
PRO AE 343318-81-0
CAT 816-43-3 LInEt2

RX(25) OF 66 ...X + Y ==> AF...



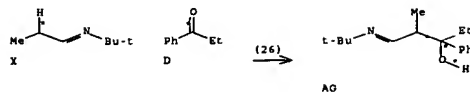
AF

143

144

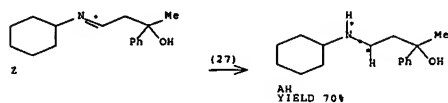
RX(25) RCT X 7020-81-7, Y 98-86-2
PRO AF 343323-16-0
CAT 816-43-3 LiNEt2

RX(26) OF 66 ...X + D ==> AG...



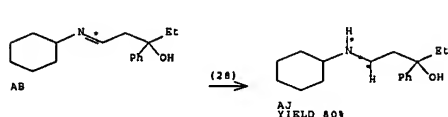
RX(26) RCT X 7020-81-7, D 93-55-0
PRO AG 343595-95-9
CAT 816-43-3 LiNEt2

RX(27) OF 66 ...Z ==> AH



RX(27) RCT Z 1217-04-5
RGT AI 16853-85-3 LiAlH4
PRO AH 343596-78-1

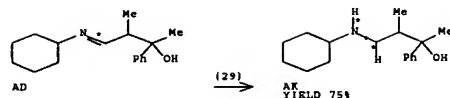
RX(28) OF 66 ...AB ==> AJ



RX(28) RCT AB 343617-82-3
RGT AI 16853-85-3 LiAlH4
PRO AJ 75243-14-0

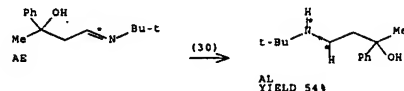
145

RX(29) OF 66 ...AD ==> AK



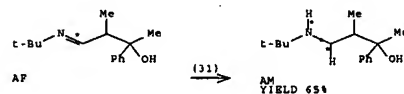
RX(29) RCT AD 1712-88-5
RGT AI 16853-85-3 LiAlH4
PRO AK 343617-70-9

RX(30) OF 66 ...AE ==> AL



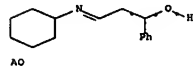
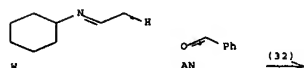
RX(30) RCT AE 343310-81-0
RGT AI 16853-85-3 LiAlH4
PRO AL 75263-07-9

RX(31) OF 66 ...AF ==> AM



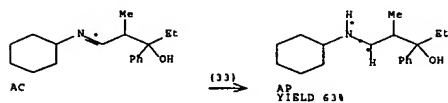
RX(31) RCT AF 343323-16-0
RGT AI 16853-85-3 LiAlH4
PRO AM 343323-15-9

RX(32) OF 66 ...W + AN ==> AO



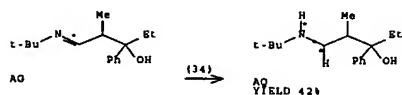
RX(32) RCT W 1193-93-7, AN 100-52-7
PRO AO 1215-49-2
CAT 816-43-3 LiNEt2

RX(33) OF 66 ...AC ==> AP



RX(33) RCT AC 343623-11-0
RGT AI 16853-85-3 LiAlH4
PRO AP 343623-09-6

RX(34) OF 66 ...AG ==> AQ



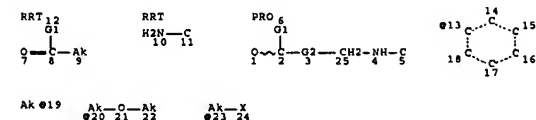
RX(34) RCT AG 343595-95-9
RGT AI 16853-85-3 LiAlH4
PRO AQ 343595-94-8

FILE 'HOME' ENTERED AT 15:33:48 ON 03 APR 2007

147

SEARCH HISTORY

=> d stat que 127; d his nofile
L15 STR



VAR G1=19/20/23/13

REP G2=(0-2) CH2

NODE ATTRIBUTES:

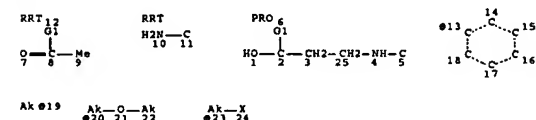
NSPEC IS RC AT 5
NSPEC IS RC AT 11
CONNECT IS E1 RC AT 1
CONNECT IS E1 RC AT 9
CONNECT IS E1 RC AT 19
CONNECT IS E1 RC AT 22
DEFAULT MLEVEL IS ATOM
OGCAT IS LOC SAT AT 9
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 25

STEREO ATTRIBUTES: NONE

****MAPPINGS****

NOD SYM ROL NOD SYM ROL
5 C PRO 11 C RRT
11 C RRT 5 C PRO
L19 150 SEA FILE=CASREACT SSS FUL L15 (722 REACTIONS)
L24 STR



VAR G1=19/20/23/13

NODE ATTRIBUTES:

NSPEC IS RC AT 5
NSPEC IS RC AT 11
CONNECT IS E1 RC AT 19
CONNECT IS E1 RC AT 22
DEFAULT MLEVEL IS ATOM
MLEVEL IS CLASS AT 1

146

148

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 25

STEREO ATTRIBUTES: NONE

****MAPPINGS****

NOD SYM	ROL	NOD SYM	ROL
5 C	PRO	11 C	RRT
11 C	RRT	5 C	PRO

L27 8 SEA FILE=CASREACT SUB=L19 SSS FUL L24 (26 REACTIONS)

100.0% DONE 219 VERIFIED 26 HIT RXNS 8 DOCS
SEARCH TIME: 00.00.03

(FILE 'HOME' ENTERED AT 14:58:38 ON 03 APR 2007)

FILE 'CAPLUS' ENTERED AT 14:58:45 ON 03 APR 2007

E US2005-520362/APPS
L1 1 SEA ABB-ON US2005-520362/AP
D SCAN

FILE 'CASREACT' ENTERED AT 14:59:40 ON 03 APR 2007

E US2005-520362/APPS
L2 12 SEA ABB-ON MICHEL D7/AU
L3 72 SEA ABB-ON 3-AMINO ALCOHOL#
L4 2 SEA ABB-ON L2 AND L3
D SCAN
L5 STR
L6 1 SEA SSS SAM L5 (12 REACTIONS)
D SCAN

FILE 'STNGUIDE' ENTERED AT 15:06:32 ON 03 APR 2007

FILE 'CASREACT' ENTERED AT 15:08:11 ON 03 APR 2007

L7 SCREEN 1215
L8 1 SEA SSS SAM L5 AND L7 (12 REACTIONS)

FILE 'STNGUIDE' ENTERED AT 15:09:47 ON 03 APR 2007

FILE 'CASREACT' ENTERED AT 15:11:33 ON 03 APR 2007

L9 STR L5
L10 1 SEA SSS SAM L9 AND L7 (12 REACTIONS)
L11 STR L9
L12 3 SEA SSS SAM L11 AND L7 (7 REACTIONS)
D SCAN
D QUS
L13 STR L11
L14 3 SEA SSS SAM L13 (7 REACTIONS)
L15 STR L13
L16 4 SEA SSS SAM L15 (33 REACTIONS)
L17 3 SEA ABB-ON L16 NOT (L12 OR L14)
D SCAN
D QUS L15

L18 27925 SEA SSS FUL L15 (367857 REACTIONS) EXTEND
L19 150 SEA SSS FUL L15 (722 REACTIONS)
SAVE TEMP L19 YOU362CASR5/A
L20 STR L15
L21 3 SEA SUB=L19 SSS SAM L20 (7 REACTIONS)
D SCAN
D STAT QUS L19
L22 STR L15
L23 8 SEA SUB=L19 SSS SAM L22 (31 REACTIONS)
D STAT QUS L21
L24 STR L20
L25 1 SEA SUB=L19 SSS SAM L24 (1 REACTIONS)
D SCAN
L26 66 SEA SUB=L19 SSS FUL L24 (219 REACTIONS) EXTEND
L27 8 SEA SUB=L19 SSS FUL L24 (26 REACTIONS)
SAVE TEMP L27 YOU362SUB1/A
L28 0 SEA ABB-ON L27 AND L4

FILE 'CASREACT' ENTERED AT 15:29:11 ON 03 APR 2007

D QUS L4
D IALL L4 1
D IALL L4 2
D STAT QUS L27
D IALL L27 1-8

FILE 'HOME' ENTERED AT 15:33:48 ON 03 APR 2007

D STAT QUS L27

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